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ARTERIOSCLEROSIS OBLITERANS. A CLINICAL AND PATHOLOGIC STUDY.

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Gangrene in the aged has been recognized since the earliest records of disease in man. It is a curious fact that for centuries gangrene did not undergo critical investigation. At best, references to this condition were brief and the conception of an obstruction in the artery by thrombosis was overlooked until the middle of the nineteenth century. Cruveilhier[7b] first described intra-arterial clots which occurred in cases of gangrene of the extremities. He erroneously ascribed the lesion in all cases to the presence of arteritis. The term "arteriosclerosis" seems to have been originated by Lobstein (1829–1833).[7a] The present conception of arteriosclerosis has been greatly influenced by the teachings of Virchow, and except for recent evidence concerning the importance of lipoid metabolism in cases of arteriosclerosis, little progress since Virchow's time has been made in solving the causation of this disease.

The nomenclature of arteriosclerotic disease of the extremities is unsatisfactory. The terms "senile gangrene" and "diabetic gangrene" should be discarded. They represent a terminal process which in no way explains the underlying pathologic lesion. "Endarteritis obliterans" is a term that was coined in 1879 by von Winiwarter,[10] who described an entirely different lesion, a form of arteritis which now is recognized as thrombo-angiitis obliterans. "Atherosclerosis" is a term used for arteriosclerosis associated with extensive formation of atheroma. It is not a distinct entity. It is important to remember that the symptoms and manifestations of arteriosclerotic disease of the extremities are produced only by

insufficiency of arterial blood. This insufficiency is, in turn, the result only of obstruction of the arterial lumens and is not the result of degenerative changes in the arterial walls. Because of this, Buerger[4] suggested the term "arteriosclerosis with occlusion," and this term has been modified to "occlusive arteriosclerosis" by some students of the subject. "Arteriosclerosis with thrombosis" is not entirely correct, inasmuch as the occlusion is caused in part by atheroma as well as by thrombosis. "Thrombo-arteriosclerosis obliterans" is a good descriptive term but is euphonically too similar to "thrombo-angiitis obliterans." We believe that "arteriosclerosis obliterans" is the best term which has been used, because it is not too long and is sufficiently descriptive of the pathologic process to which it alludes.

Material. This paper is based on a clinical study of 280 consecutive cases of thrombo-arteriosclerosis obliterans which were observed at The Mayo Clinic in the years 1929 to 1933, inclusive. Undoubtedly, milder clinical forms have been overlooked in which one or more arteries of the extremities were involved without production of symptoms. Routine examination usually does not include determination of the presence or absence of pulsations in the peripheral arteries. Follow-up letters were sent to patients 3 years after the time of their first visit to the clinic.

The clinical data have been supplemented by detailed gross and histologic studies of the arteries obtained from 32 legs that were amputated because patients had arteriosclerosis obliterans. It is obvious that the lesions encountered in these legs represented for the most part end-stages in a pathologic process which had been present for many years. However, in a number of instances the advanced lesions were localized and it was possible to identify other lesions which we felt represented earlier stages of the condition.

Etiology. Arteriosclerosis obliterans occurs predominantly among men between the ages of 50 and 70 years. In the 280 cases, 240 of the patients were men and 40 were women, a ratio of 6 to 1. A similar sex ratio has been noted for coronary thrombosis, and by Allen[2] for a number of other diseases. This difference, however, is not so marked in cases of arteriosclerosis obliterans as it is in thrombo-angiitis obliterans, which has an incidence among women of less than 2%. The youngest patient in this series was 35 years of age and the oldest 96; 70% of the patients were between the ages of 50 and 70.

There is no significant difference in the racial incidence of the disease. Twenty (8.3%) of the 240 patients in whose history there was a statement of nationality, were Jews. This may be contrasted with a distribution of approximately 30% of Jews among the patients who have thrombo-angiitis obliterans and who come to the clinic. All the usual races found in the United States were represented in the group. The highest incidence of the condition was among the native-born Americans.

The most obvious causative explanation of the pathologic changes in arteriosclerosis of any part of the body is that of Virchow; the

presence of such changes represents wear or aging of arterial tissue as a result of stress and strain. Arteriosclerotic lesions are found with great frequency in the aorta and at the orifices of the branches of the aorta, structures that are subject to more than average degrees of intravascular strain, both constant and intermittent. Also, it is well established that arteriosclerosis develops prematurely among patients who have arterial hypertension. The fact that arteriosclerosis obliterans is so rare and so much less severe in the upper extremities than it is in the lower extremities may be explained by the fact that blood pressures are normally higher in the lower than in the upper extremities. It is obvious that there must be considerable hereditary differences in the ability of the arterial tissue to stand stress and strain, and this may apply not only to the arterial tree as a whole but to certain specific parts of the arterial tree.

Controversy exists as to whether the development of arteriosclerosis is entirely dependent on this hereditary weakness of the arterial tree plus stress and strain alone or whether other influences, chiefly certain metabolic and chemical disturbances of the body, might accelerate the development of the lesions if not actually cause them. Leary[6] and others have expressed the opinion that the atheromatous lesions of human beings may develop as a result of a disturbance in fat or cholesterol metabolism. The reasons for this are as follows:

1. Cholesterol and fat are constantly present in rather large amounts in the atheromatous plaques, even in the earliest stages of the development of such plaques. At the deep margin of the plaque there are often numerous lipophages in various stages of degeneration and destruction. Thus, the atheroma is very similar, histologically, to xanthomatous lesions, particularly those of the nodular type.

2. Atherosclerotic lesions, said to be indistinguishable from atherosclerotic lesions which affect human beings, can be produced in rabbits by feeding animal fat or cholesterol. In these instances severe lipemia and hypercholesterolemia develop as a result of the inability of the rabbits to metabolize animal fat successfully.

3. Arteriosclerosis obliterans is more common among persons who have diabetes and particularly among those who have ingested high fat diets than among persons who do not have diabetes, and it occurs prematurely among persons who have diabetes (this point is somewhat controversial).

4. In xanthoma tuberosum, a condition which is characterized by severe lipemia, and in a few isolated instances of lipemia unassociated with cutaneous xanthoma, the incidence of arteriosclerosis obliterans and coronary sclerosis has been high and the lesions have been rather extensive.

5. Studies on patients who had coronary and peripheral arterio-

sclerosis have shown that in many instances there is some increase in the quantity of the blood lipoids over that found in control subjects. This is more common among patients in the fifth and sixth decades of life than among older patients.

Data available at the present time would indicate that lipemia, even of mild degree, may accelerate the development of arteriosclerotic lesions but that it is doubtful that lipemia is a more important factor in the inception of such lesions than are stress and strain.

Pathologic Findings. The lesions of the arteries consisted essentially of three components (Figs. 1, 2 and 3): 1, atheromatous plaques in the subintimal tissue; 2, degenerative changes occurring in the medial coat; and 3, thrombosis. These three components of the lesion were present in unequal degree in different cases. Proliferation of elastic tissue between the intima and media was seen in very early lesions. More commonly the earliest lesion found was a small atheroma. In its earliest stages an atheroma appeared grossly as a slightly raised yellowish plaque on the endothelial surface of the artery. Histologically, there was a thickening between the internal elastic lamina and the endothelial layer which consisted of proliferated endothelial cells, fibroblasts, lipophages (foam cells) and considerable neutral fat (Fig. 4*a*). Advanced atheromatous lesions were often seen; they projected into the lumen for a considerable distance and partially but never completely occluded it. They were always relatively acellular and contained irregularly distributed deposits of fat globules, cholesterol, lipophages (Figs. 1, 2, 4*b* and 5), fibrous and hyaline tissue.

Thrombi were seen in all cases. They were always associated with formation of atheroma (Figs. 1, 2 and 5), although there was no relationship to the size or extent of the atheromas. The thrombi often completely occluded the lumen and they were often of various ages. Usually, layers of thrombotic lesions were seen in various stages of organization. In advanced lesions it was difficult at times to be certain of the character of the occluding mass, because organization and canalization of a thrombus simulated closely the appearance of atheroma.

In the medial coat the earliest degenerative changes which were noted were localized atrophy of the muscle fibers and replacement by collagenous fibers and proliferated collagenous connective tissue. Localized calcification was noted in many but not all of the arteries studied. In advanced lesions the entire muscular coat was found to be irregularly thinned and replaced in part by relatively acellular fibrous and hyaline tissue with or without deposition of calcium. In a few instances complete rings of calcium deposits were found similar to those seen in the so-called Mönckeberg's sclerosis.

No significant differences were noted in the lesions of arteriosclerosis obliterans among diabetic and non-diabetic patients. Thrombosis occasionally was seen in large veins (femoral, popliteal,

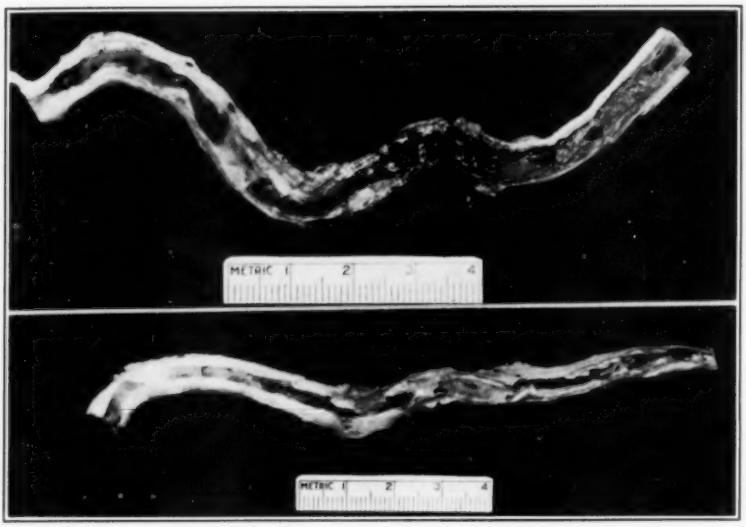

FIG. 1.—Popliteal arteries obtained from 2 patients who had arteriosclerosis obliterans (formalin and bisected longitudinally). Irregular atheromatous deposits (white) and thromboses of various ages (gray and black) are seen.

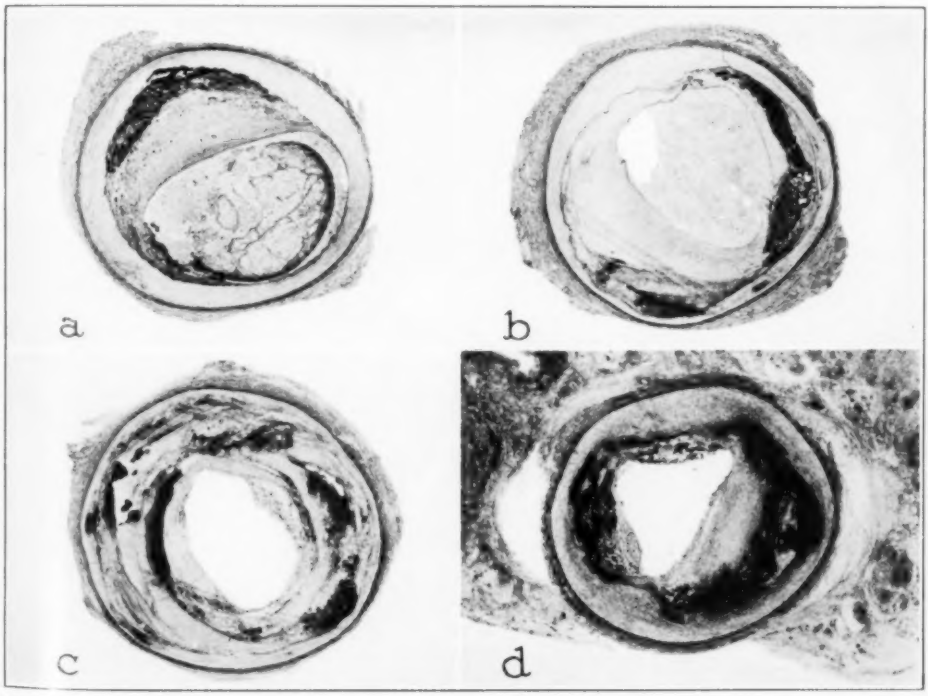

FIG. 2.—Cross-section of arteries (Sudan III and hematoxylin); *a*, popliteal artery (×10) in which there is one small portion of calcification; otherwise, the medial coat is not much damaged; the lumen is partly occluded by an atheromatous plaque and partly occluded by an organized thrombus; the outer portion of the atheroma contains a large amount of fat; *b*, popliteal artery (×10) in which the black deposits are fat; one may note irregularity of thickness of medial coat and splitting of internal elastic lamina; two stages of organized thromboses are shown; *c*, advanced atheroma and advanced degeneration of arterial wall of popliteal artery (×11); *d*, posterior tibial artery (×16) in which the black material is fat and indicates extensive formation of atheroma.

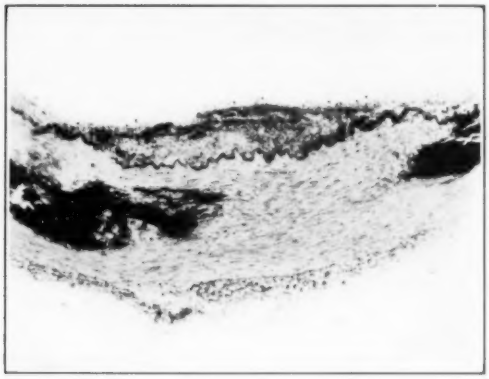

Fig. 3

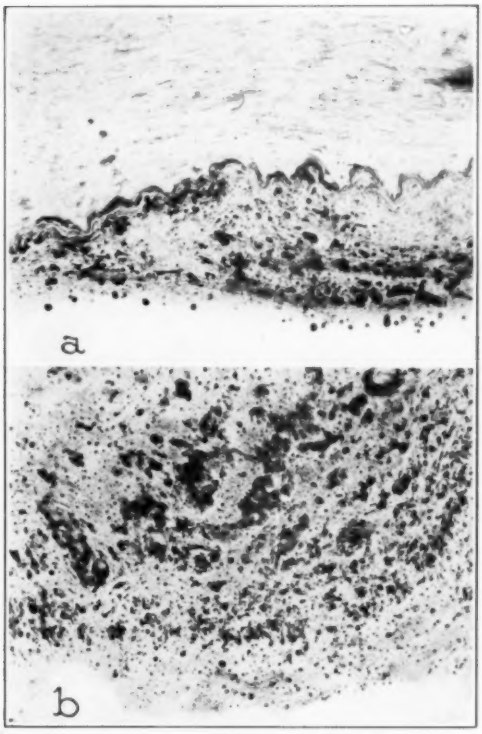

Fig. 4

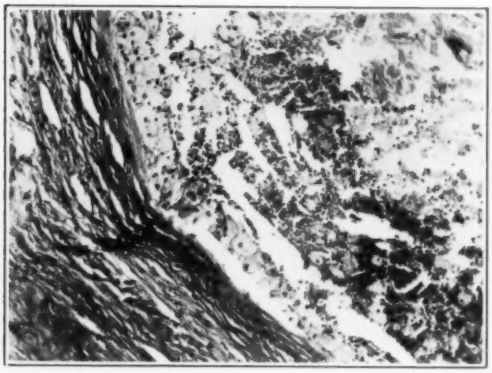

Fig 5

posterior tibial) in cases of advanced arteriosclerosis obliterans or in association with acute and extensive arterial thrombosis.

The pathologic picture of arteriosclerosis obliterans is quite different from that of thrombo-angiitis obliterans and there should be no difficulty in distinguishing these two lesions. The important differential points are given in Table 1.

TABLE 1.—ARTERIOSCLEROSIS OBLITERANS AND THROMBO-ANGIITIS OBLITERANS: DIFFERENTIAL PATHOLOGIC FEATURES.

	Arteriosclerosis obliterans.	Thrombo-angiitis obliterans.
Medial coat	Marked degeneration with irregular thinning, fibrosis, hyalinization and sometimes calcinosis	Fibroblastic proliferation, but no degeneration and no calcinosis
Subintimal layer	Extensive atheroma formation with fat and cholesterol	No atheroma, no fat, no cholesterol
Thrombus	Often incomplete, with irregular and relatively acellular organization	Usually complete, with very cellular organization

Certain changes were noted in other tissues of the legs, and these changes were thought to be the results of ischemia. Often, atrophy of the skeletal muscles with replacement in part by fatty deposits or by fibrous tissue was present. In many cases there was considerable absorption of subcutaneous fat from the feet and toes. There were often thinning and atrophy of the skin and osteoporosis of the bones. Extensive Wallerian degeneration and fibrosis of the nerve trunks—ischemic neuritis—as described by Priestley,[8] were frequently seen. The gangrenous lesions were not materially different from any type of ischemic gangrene or gangrene resulting from ischemia plus trauma.

A recent interesting observation (Winternitz[11]) on the pathologic anatomy of generalized arteriosclerosis has shown that lesions of the arterial walls are often overvascularized rather than undervascularized and that, apparently, foci of degeneration of the arterial wall may be initiated by hemorrhages into various portions of the arterial coats. These hemorrhages eventually may become calcified and give rise to the typical deposits of calcium which are seen in the medial coat. However, in arteriosclerosis obliterans, calcification and other forms of degeneration of the medial coat have no clinical significance in themselves, inasmuch as they do not cause significant interference with the flow of the blood (Fig. 3). Actual

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LEGENDS FOR FIGS. 3, 4 AND 5.

FIG. 3.—Cross-section of posterior tibial artery. Extensive calcification of medial coat. Small atheroma. There was no thrombosis in this artery (×55; H. and E.).

FIG. 4.—Cross-sections of posterior tibial artery (Sudan III and hematoxylin; ×125); *a*, early atheroma, showing deposits of fat (black) many of which are in lipophages; *b*, advanced atheroma, showing lipophages and fat globules.

FIG. 5.—Cross-section of atheroma of popliteal artery (H. and E.; ×125), showing foam cells (lipophages) at margin of atheroma and fresh thrombosis.

obstruction of the artery is begun by the atheroma and is completed by the thrombosis, and it is the degeneration and roughening of the inner surface of the atheroma which provide for the development of the thrombus. It is possible that other factors, such as alterations in the condition of the blood (polycythemia and thrombophilia), augment the development of these thrombi. It is doubtful, however, that in the swiftly moving arterial stream a thrombus ever forms without the presence of some lesion of the arterial intima as a starting point. Therefore, the most important component of the lesion present in arteriosclerosis obliterans seems to be the atheromatous plaque, because this plaque is responsible in itself for partial occlusion of the lumen and is the locus for the development of the thrombus which completes the occlusion.

Symptoms. Symptoms of arteriosclerosis obliterans of the legs are referable to diminished blood supply to the muscles, nerves and other tissues. The onset may be gradual or sudden. If the condition is chronic, intermittent claudication usually is the first symptom noted and it may persist for years without the appearance of other symptoms. The patient may be aware of an increased tendency of the foot to become cold, atrophic changes in the nails, or slowing of the growth of the nails. When the occlusive process is in the upper part of the femoral artery or in the iliac arteries and when it follows sudden occlusion of smaller arteries, ischemic neuritis may develop. The pain of ischemic neuritis has certain characteristics that aid in diagnosis. It is usually paroxysmal in nature and extends over or involves most of the leg or foot. The paroxysms are worse at night. Vasospastic changes in color occasionally accompany the bouts of pain and in some cases petechiæ appear in the skin over the painful region. The pain usually is influenced by position and usually is not influenced by the application of heat. Objective neurologic changes are rare and are found only in the most severe instances of the condition. In such cases, hyperesthesia, anesthesia, paralysis and loss of reflexes may occur. Paresthesia usually is not a primary complaint of patients who have arteriosclerosis obliterans. The occurrence of paresthesia in the absence of definite signs of arterial insufficiency is not sufficient reason for making a diagnosis of arteriosclerosis obliterans, because the paresthesia is more likely to be the result of vascular or senile changes in the central nervous system than of arteriosclerosis obliterans. As the occlusive process progresses, spontaneous gangrene or ulceration may develop; it usually occurs in the toes but may extend to the foot. More rarely, spontaneous gangrene or ulceration may begin on the skin of the lower part of the leg. In approximately 50% of cases the ulceration or gangrene is initiated by trauma, in the form of some crushing injury, laceration, wound, or in the form of thermal injury, such as a burn or frostbite, or in the form of chemical injury, often resulting from local medicinal applications.

Distribution of Lesions. The disease is usually bilateral, but at any stage its development is usually unequal; thus, the signs of circulatory insufficiency are more noticeable in one leg than in the other. Absence of pulsations in the posterior tibial, dorsalis pedis and popliteal arteries is the rule and in many instances pulsations are absent in the femoral artery in Scarpa's triangle. Pallor of the extremities on elevation and excessive rubor on dependency, particularly if these changes are unequal and if there is a definite delay in the return of color on dependency after elevation, are valuable signs of arterial insufficiency. There are often rather noticeable atrophy of the subcutaneous tissues and muscles of the calf and a shrunken appearance of the toes. These changes are more conspicuous as a rule in patients such as we are considering than they are in patients who have comparable degrees of arterial insufficiency caused by thrombo-angiitis obliterans. The first clinical evidence of arteriosclerosis obliterans may be the occurrence of sudden arterial occlusion caused by extensive thrombosis.

There is a marked difference in the presence of occlusion of the arteries of the upper extremity and of occlusion of the lower extremity. In only 3 instances in our series of cases was either the radial or ulnar artery occluded. About one-half of the patients who have thrombo-angiitis obliterans have occlusion of arteries of the arm. The rarity of occlusion of arteries of the arm in arteriosclerosis obliterans, as compared with thrombo-angiitis obliterans, is an important point in differentiating these two diseases. In 92 (67%) of the 137 cases in which the ocular fundi were examined, sclerosis of the retinal arteries or arterioles was present.

Calcification and Occlusion of Arteries. In a number of cases only one extremity had been affected by occlusion. This observation afforded an opportunity for us to study by roentgenography the amount of calcification present in the occluded and the non-occluded extremity. No direct relationship was found between the extent of calcification and thrombosis with occlusion. Calcification usually was as marked and as extensive in the non-occluded extremity as it was in the occluded extremity. However, a marked difference in the frequency of calcification existed between the sexes. The incidence of calcification among men was 69% and among women 31%.

Diabetes Mellitus. Diabetes mellitus was diagnosed in 57 (20.3%) of the 280 cases. This value may be somewhat low, because milder grades of diabetes may be overlooked if a glucose tolerance test is not performed. In 50 (31.8%) of the 157 cases in which the value for the blood sugar was determined the values were more than 120 mg. per 100 cc.

Incidence of Trophic Ulcers and Gangrene. Ulceration was present in 76 of the 280 cases and frank gangrene in 76, an incidence of 54% of the group studied. Among the patients who had diabetes,

the incidence of ulcers and gangrene (76%) was greater than among the patients who did not have diabetes. The majority of the diabetic patients had an extensive moist type of gangrene, secondary infection and frequently systemic reactions.

Ulceration and gangrene, when they occur, are usually of the dry type and are usually accompanied by little or no systemic reaction. Comparatively less pain is present than that which accompanies thrombo-angiitis obliterans. However, when diabetes is associated, the lesions exhibit a tendency to be moist and infected, considerable systemic reaction may be present and rapid development of ascending lymphangitis and septicemia may occur. In cases of the type under consideration, there seems to be a greater tendency for arteriosclerotic gangrenous and ulcerative lesions to spread and a lesser tendency for them to heal, than is the case with lesions of thrombo-angiitis obliterans, probably because of the fact that age has also impaired the vitality and resistance of the tissues.

Ischemic Neuritis and Paresthesia. Ischemic neuritis was noted in 22 (about 8%) of the cases. Numbness, tingling and hyperesthesia were the usual subjective complaints. Paresthesia was a significant complaint in 14 cases (5%). When it occurred, it was as likely to be present in an extremity with no occlusion as in an extremity with occlusion.

Hypertension. Hypertension, that is, a diastolic value of 90 mm. of mercury or more and a systolic pressure of more than 150 mm. of mercury, was found in 99 (35%) of the cases. This incidence undoubtedly is low, because many of the patients studied had a latent form of hypertensive disease or had had hypertension as demonstrated by the changes in the retinal arterioles. It is not uncommon to observe hypertensive changes in the retinal arterioles with normal or subnormal values for the blood pressure. The reactions of such patients to the cold pressor test indicate that hypertension exists in a latent form. Some patients undoubtedly have had elevations of blood pressure which have decreased to lower values following enforced rest and exhaustion and the use of drugs. In 18 cases of this group, the blood pressure was normal, but retinal findings indicated hypertensive changes. Including patients of this group, the incidence of hypertensive vascular disease in this series of cases was about 42%.

Diagnosis. The diagnosis of arteriosclerosis obliterans depends, first, on establishment of definite evidence of organic arterial insufficiency of one or both lower limbs. Almost all instances of chronic occlusive arterial disease of the lower limbs are caused by either thrombo-angiitis obliterans or arteriosclerosis obliterans, and in the great majority of instances if the first symptoms or signs appear after the patient is 50 years old, arteriosclerosis obliterans is responsible. However, in our series of cases the disease developed as early as the thirty-fifth year in 1 case. Other features which favor acceptance

of the diagnosis of arteriosclerosis obliterans over that of thrombo-angiitis are the absence of involvement of the upper extremities, the absence of superficial phlebitis, the presence of diabetes mellitus, the presence of hypertension, and the presence of roentgenologically demonstrable calcification of the arteries. A search for calcification should include the making of roentgenograms of the thigh and pelvis as well as of the lower leg. The presence of calcification is not *per se* evidence of arteriosclerosis obliterans or impaired circulation of the extremities. It is of importance only in differentiating between the different types of occlusive arterial disease. Roentgenologically demonstrable calcification is absent in approximately 30% of instances of arteriosclerosis obliterans. It may occur to a slight degree in the presence of thrombo-angiitis obliterans.

In case of doubt, the determination of the concentration of plasma lipoids may be of some help in the differential diagnosis of thrombo-angiitis and arteriosclerosis obliterans. Cholesterol values in the plasma in excess of 250 mg. and total lipoid values in excess of 650 mg. per 100 cc. favor the diagnosis of arteriosclerosis obliterans, particularly among patients in the borderline age groups. The values for plasma lipoids are not likely to be materially elevated in the aged, whether or not such persons have arteriosclerosis obliterans.

Prognosis. Persons who have arteriosclerosis obliterans have a shortened expectancy of life. Of the 116 patients concerning whom satisfactory follow-up information was obtained, 54.6% died within 3 years of their first visit to the clinic. The majority died in a manner which was suggestive of coronary thrombosis as the cause of death. Several causes are responsible because: 1, arteriosclerosis is a generalized disease and advanced degenerative foci may be present in arteries in other and more vital parts of the body; 2, the presence of diabetes and advanced grades of moist gangrene and cellulitis is accompanied by a fairly high medical and surgical risk; 3, persons who have advanced forms of arteriosclerosis are susceptible to intercurrent infections and the bronchial pneumonia of the aged.

It is interesting that in our series the mortality rate was not appreciably higher in the group of patients who had diabetes than it was in others. This was true in regard to both the group of patients who underwent amputation at the clinic and the group of patients whose condition was followed up after they left the clinic.

Of the 70 patients who required amputation, 24 had diabetes; of the latter group 1 died following operation, a mortality rate of 4.1%, as compared with 4.3% for the entire group. The most common cause of death following surgical amputation is some type of vascular accident. In another series of cases of diabetes studied by Allan and Kintner,[1] there was a surgical mortality rate of 9.3% following amputation in 86 cases. The study of these cases brought out the significant fact that patients who have arterio-

sclerosis obliterans and diabetes were subject to a mortality rate of 20% when amputation was done below the ankle and 7% when it was done through the lower part of the thigh or upper third portion of the leg. Secondary amputation was required in only 4 cases in the group studied by Allan and Kintner. In contrast to this, in 69 cases of gangrene and infection of the foot in which the patients were treated medically the mortality rate was 23%. The dictum "either operate early or operate high if diabetes is present" should be respected.

Treatment. The limited expectancy of life of patients who have arteriosclerosis obliterans should modify methods of treatment; it is one of the major reasons for not carrying out sympathetic ganglionectomy for these patients. Such measures as fever therapy should be used with extreme caution, if at all, although the intramuscular injection of sulphur may be used safely. Treatment should consist of prophylactic measures, methods to increase circulation, control of pain, and local measures to control ulceration and infection.

Prophylactic Measures. One of us (Barker[35a]) found that in 56% of a group of patients who had arteriosclerosis obliterans, ulceration or gangrene had been induced by accidental trauma or by injudicious therapeutic procedures. In 62% of the group of patients who had induced gangrene, amputation of a leg was necessary. Protection and proper care of the feet are of prime importance. Every effort should be made to avoid trauma to the toes or feet of the patient. New shoes should be "broken in" gradually. Felt shoes and heavy woolen stockings should be worn in cold weather. Chiropodic treatment should be administered with great care and with full allowance for the inadequate circulation present. Strong disinfectants and chemical compounds should never be applied to the feet. Local heat to preserve the warmth of the feet should be used with caution and preferably with the heating unit placed at some distance from the extremity. Trichophytosis should be treated with mild measures. Soaking the feet in a 1 to 8000 solution of potassium permanganate is safe and usually effective for the aforementioned condition. The use of tobacco should be discouraged because of its vasoconstrictor effect. When an elevation in the value for plasma lipoids is present, it is usually advisable to have the patient ingest a diet low in animal fats. This diet should consist of carbohydrate 420 gm., protein 60 gm., and fat 30 gm., of which 15 gm. may be animal fat. The diet should be supplemented by ingestion of 1 capsule of haliver oil a day. In a series of cases studied by one of us (Barker[35b]) there was a definite reduction in plasma lipoids in approximately one-half of the patients who had ingested this diet. It also may be possible to reduce the value for plasma lipoids by the careful administration of desiccated thyroid glands.

Measures to Increase Circulation. One of the main objectives in the treatment of occlusive vascular disease is to produce vasodilatation in that part of the vascular system still capable of expanding and thus to increase the blood supply to the affected extremity. Heat has long been known to produce vasodilatation. This may be applied locally in the form of radiant heat or to a distant part of the body as in the method of Gibbon and Landis.[5] In using any form of heat applied directly to the leg, great care should be taken to avoid having the temperature above 105° F. (40.5° C.) Postural exercises as designed by Buerger and Allen can be carried out easily by the patient and are of definite value in increasing the circulation. A mechanical oscillating bed has been devised which enables the patient to carry out the principle of the postural exercises without effort. The only advantage of this mechanical device is that it allows a more prolonged period of exercises than can be carried out by the patient. Short-wave diathermy applied to the trunk is of value in producing vasodilatation. However, it should be applied only by individuals trained in its application as the high frequency current may be dangerous if not properly used.

The production of fever by artificial means is one of the best methods of producing vasodilatation. The administration of typhoid vaccine is not advisable for most patients who have arteriosclerosis obliterans, because the reaction to foreign protein may not be well tolerated. An intramuscular injection of 1 or 2 cc. of olive oil containing 2% of sulphur in suspension is a safer method of producing fever than the administration of typhoid vaccine but has the disadvantage of causing considerable pain at the site of injection; however, this can be obviated partially by injecting from 1 to 5 cc. of a 1% solution of procaine with the sulphur-in-oil. Silbert[9] and others have treated many patients who had arteriosclerosis obliterans with intravenous injections of hypertonic solution of sodium chloride but have not felt that their results were as good as those obtained in similar treatment of patients who had thrombo-angiitis obliterans. In a warm environment, the use of mechanical methods of treatment such as intermittent suction and pressure or intermittent venous compression and the oscillating bed may improve the circulation. These methods were not in use during the time the group of patients under consideration was treated at the clinic; consequently, we were unable to evaluate the results of mechanical methods of treatment in this study. There is considerable difference of opinion as to the efficacy of this type of treatment. Certainly in most of our cases of arteriosclerosis obliterans in which efficient but safe methods of treatment are needed, mechanical methods have not been of as much help as was at first anticipated. Sympathectomy should be considered for the younger patients. The two-stage operation through a lumbar approach is preferable in cases of arteriosclerosis obliterans.

Treatment of Pain. Pain may be of two types, that is, intermittent claudication or rest pain. Patients who have no symptoms other than intermittent claudication have received extracts of pancreatic and muscle tissue intramuscularly with a subsequent increase in the distance they are able to walk, in many instances. A good plan for administering these extracts is to inject 3 cc. at each dose, once a day for 1 week, then twice a week for 4 weeks, and then once a week for 4 weeks.

Rest pain, particularly that of ischemic neuritis, may be very difficult to control. Alcoholic drinks equivalent to about 1 ounce of ethyl alcohol with 10 to 20 gr. (0.65 to 1.3 gm.) of acetylsalicylic acid is frequently as effective as any anodyne. Administration of opiates may have to be resorted to in some instances. Various mechanical methods of treatment, particularly the oscillating bed, may be of help in relieving rest pain. If simple measures do not relieve severe rest pain, section or crushing of the peripheral nerves of the leg may be performed. In some instances, this measure may afford enough relief of pain to delay amputation and allow prolonged trial of medical treatment. Intraspinal injection of alcohol may be tried as a last resort. If the pain is intractable, it may be wiser to amputate a limb rather than to subject a patient, whose expectancy of life is already limited, to a period of prolonged suffering and disability.

Treatment of Ulceration and Gangrene. For patients who have ulceration or gangrene limited to the toes, rest in bed is important. Warm foot baths at temperatures not exceeding 105° F. (40.5° C.) are useful in promoting drainage and allaying infection. Strong antiseptics should not be employed in the solution used for the foot soaks. A saturated solution of boric acid is usually satisfactory. A 0.5% solution of chloramine or a solution of potassium permanganate 1 to 8000 or weaker may be used. The period of soaking should be short and may be repeated several times a day. Warm packs, if applied cautiously, may be used when much infection or edema is present, but foot baths are preferable because of the danger of harming the ischemic tissues by other methods. When infection has abated and healing is beginning, a 1 to 1000 solution of thioglycerol may promote the formation of granulation tissue.

General Measures. It is important to maintain the patient's general health and resistance by rest, proper diet and treatment of anemia if it is present. Diabetes should be carefully controlled. If polycythemia vera is present, appropriate measures should be directed against it.

Treatment of Sudden Occlusion. When sudden occlusion of an artery occurs, emergency measures should be instituted. Any unnecessary delay endangers the chances of recovery of the patient.

The situation is somewhat like that of diabetic coma and the physician should remain in constant attendance until there is relief or an unfavorable outcome. Opiates should be administered at once to control pain. Alcoholic drinks usually are beneficial in relieving pain and may aid also by relieving arterial spasm. The head of the bed should be elevated and the leg placed in a dependent position in order to use the effects of gravity in increasing circulation. The limb should never be elevated. The extremity should be wrapped in cotton, which can be held in place by a roller bandage, to conserve its natural warmth. Heat may be applied by using a cradle with an incandescent bulb in it. Great care should be taken to avoid excessive heat. The temperature of the air about the extremity should be maintained at about 32.2° C. (90° F.). Heat never should be applied directly to the skin. A vasodilator should be administered to relieve arterial spasm when it is present. Papaverine hydrochloride, a vasodilator, administered intravenously in doses of ½ gr. (0.032 gm.) may produce improvement in circulation. If improvement in circulation is noted (usually within a few minutes), the injection may be repeated in 4 to 6 hours. Care should be taken to see that the papaverine is active physiologically.

In cases of acute arterial occlusion there is grave danger of extension of thrombosis; consequently, intravenous infusion of heparin is a justifiable procedure as this is the only method which will certainly prevent thrombosis. If embolectomy is performed, heparin will prevent the thrombosis which may follow incision and suturing of an artery. The intermittent use of negative and positive pressure has been employed successfully in some cases as has the oscillating bed operated in a "hot room" in which temperature is maintained at 32.2° C. (90° F.). Such mechanical methods should be used when available. In using the oscillating bed, it should be adjusted carefully so that there is a definite return of color to the foot during dependency.

Amputation. Conservative treatment may be of no avail in many cases, and amputation must be done, preferably before the patient's general condition has declined. Amputations of toes are likely to result in non-healing wounds, increase of pain and necessity for subsequent higher amputations, and are therefore rarely advisable in cases of arteriosclerosis obliterans. The prognosis for the healing of gangrenous lesions in this disease is so poor that it is probably wisest to amputate in the majority of cases if employment of conservative treatment for a few weeks has not resulted in definite improvement or in cases in which pain cannot be controlled and in cases in which gangrene has extended into the foot. Amputation of the extremity below the knee may not be successful, and if a second amputation is necessary, there is a considerable increase in operative risk. Furthermore, as has already been

pointed out, expectancy of life in this group of patients is limited. Hence, if amputation is done at all, it is usually advisable to amputate above the knee. Diabetes mellitus, when present, should be rigidly controlled. The problem of gangrene in arteriosclerosis obliterans in the presence of diabetes is definitely more complicated than in other cases because infection and septicemia may develop rapidly. When gangrene is present in patients who have associated diabetes, it is not advisable to delay, for a long time, performing amputation; when amputation is done, it should be done above the knee.

Seventy (25%) of our series of cases underwent amputation of a leg at the clinic because of the presence of frank gangrene with or without diabetes. Amputation usually was performed as quickly as conditions would permit. The aforementioned percentage does not produce the correct ultimate figure because amputation was necessary for at least an additional 5% of patients shortly after their dismissal. It seems likely that at least one-third of the patients who have thrombo-arteriosclerosis obliterans lose one limb. This does not include patients who should undergo amputation but for whom it is contraindicated by an excessive surgical risk. In these patients death ensues within a short time.

Summary. A clinical study has been made of 280 consecutive cases of arteriosclerosis obliterans which were observed at the clinic. The clinical data have been supplemented by detailed gross and histologic studies of the arteries obtained from 32 legs that were amputated because patients had arteriosclerosis obliterans. The disease was found to occur predominantly among men between the ages of 50 and 70 years. There was no significant difference in racial incidence. The possible rôle of certain metabolic and chemical disturbances as etiologic factors has been emphasized. The lesions found in the arteries which were examined for pathologic changes consisted essentially of three components: 1, atheromatous plaques in the subintimal tissue, 2, degenerative changes in the medial coat, and 3, thrombosis. No significant difference was noted in the lesions of arteriosclerosis obliterans among diabetic and non-diabetic patients. The diagnosis and treatment are discussed in detail.

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HEART SIZE AND EXPERIMENTAL ATHEROMATOSIS IN THE RABBIT.*

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The relationship between cardiac hypertrophy and coronary sclerosis is still controversial, and much of the evidence in clinical and autopsy data fails to distinguish the possible effect of the associated conditions which might produce hypertrophy from the effects of coronary sclerosis *per se*. This has led Aschoff[3] to regard hypertrophy in senescence as independent of arteriosclerosis, and has caused Bell and Clawson[5] to maintain that coronary disease itself does not cause hypertrophy of the heart. The latter authors in fact suggest that it is more reasonable to believe that the development of coronary sclerosis in the course of hypertension tends to prevent further cardiac hypertrophy. Nathanson[18] could find no relation between the degree of myocardial fibrosis and heart size in 113 autopsied cases of coronary sclerosis and attributed all the cases of large hearts in his series to preëxisting hypertension. Likewise, Lisa and Ring[15] could not find any correlation between coronary disease and cardiac hypertrophy. Sutton and Davis[26] did not obtain any cardiac hypertrophy in dogs, followed for periods up to 319 days after experimental ligation of the coronary artery producing myocardial infarction. Horine and Weiss[12] found no evidence of cardiac hypertrophy in 20 patients followed clinically from 1 to 10 years subsequent to myocardial infarction, and Miller and Weiss[17] failed to find cardiac enlargement in 19 cases of advanced coronary sclerosis.

On the other hand, Stewart[25] observed cardiac hypertrophy after producing injury of the heart muscle by repeated injections of epinephrine. Further, the enlargement of the heart observed in cases of arterio-venous aneurysm was attributed by Lewis and Drury[14] to a deficient nutrition of the myocardium; and they postulated that this mechanism might cause cardiac enlargement in

* Aided by the A. D. Nast Fund for Cardiac Research.
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coronary vascular narrowing. It is now well established that anemias lead to cardiac hypertrophy.[9,16] The hypertrophy occuring in anemia, epinephrine and arterio-venous aneurysm, however, may result from the increased work of the heart present in these conditions. Apropos of this discussion, cardiac enlargement is known to occur in cases in which the left coronary artery originates from the pulmonary artery.[1,6,11] As to coronary disease, Parkinson[21] concluded that in 8.6% of a total of 128 cases, cardiac infarction appeared to be the sole factor causing enlargement of the heart, and Palmer[20] noted that coronary sclerosis sometimes resulted in cardiac enlargement, which was progressive at times. Bartels and Smith[4] found gross hypertrophy in 88% of 42 autopsied cases following coronary occlusion. However, Davis and Blumgart[7] noted little or no hypertrophy with lesser degrees of coronary sclerosis; a slight to moderate degree of hypertrophy with more advanced sclerosis; and a considerable increase in size with the advent of congestive heart failure. In 11 patients with arteriosclerotic heart disease and no evidence of failure, Nemet and Gross[19] found 7 with heart weights less than 400 gm., 2 with weights above 400 gm., and 2 showed generalized microscopic hypertrophy of muscle fibers.

Recently Shohet *et al.*[23] in an analysis based on 122 necropsy cases without other possible causes for cardiac hypertrophy, found that coronary sclerosis produced hypertrophy of the heart, the heart weight being a function of the degree of coronary sclerosis. Smith[24] noted that right ventricular hypertrophy could be demonstrated in dogs at necropsy after ligation of the anterior descending branch of the left coronary artery, while left ventricular hypertrophy could be shown at necropsy when the smaller branches of the left coronary artery were ligated. Leary[13] made the incidental observation that following the production of atherosclerosis in rabbits some of the hearts appeared definitely enlarged.

In view of this contradictory evidence it was decided to put the possibility of a relationship between cardiac hypertrophy and coronary sclerosis to a direct experimental test. For this purpose rabbits were selected, since it has been established that the production of atherosclerosis in this animal is a relatively simple procedure, and as Anitschkow[2] and Leary[13] have pointed out, the atherosclerotic process in the rabbit is generalized and includes definite coronary artery involvement.

Method. The experiments were carried out on 30 rabbits all less than 6 months of age with body weights varying between 820 and 2100 gm. For the production of atherosclerosis a high cholesterin diet was utilized, prepared by dissolving 25 gm. of cholesterin* in 500 gm. of cottonseed oil. One hundred ten cc. of this mixture was added to each 500 gm. of cracked wheat, oatmeal or barley with added powdered brewer's yeast or a vitamin

* We are indebted to Dr. D. Klein of the Wilson Laboratories for supplying us with some of this material.

B concentrate* preparation to prevent any B avitaminosis. The animals were allowed as much of this mixture as they desired. In addition to the cholesterin feedings the animals were given fresh green vegetables twice weekly.

All the rabbits were kept on this diet for periods varying up to 4 months, at the end of which time those that survived were sacrificed. As controls 10 untreated rabbits were used. They were in the same age group and their body weights ranged from 675 to 2160 gm. Of the original 30 rabbits 8 died from intercurrent circumstances within 2 weeks after being placed on the special diet, and since gross and microscopic examination failed to reveal evidence of atherosclerosis, they were added to the 10 untreated rabbits making a total of 18 rabbits for the so-called control untreated group, Group A. Of the remaining 22 rabbits, 6 failed to develop gross or microscopic evidence of atherosclerosis after long continued cholesterin feeding (1 to 2½ months), and these therefore constituted a second so-called control treated group, Group B, which could be used to check the effect of the regimen. The remaining 16 rabbits which died from 1 to 4 months after the diet was started or were sacrificed after 4 months, all manifested atherosclerosis at necropsy which was graded arbitrarily according to degree, number and confluence of the subendothelial patches in the aorta as 1 to 4+. These animals constituted the so-called experimental group, Group C.

In every animal after death the heart and aorta were opened and carefully examined; the former for enlargement, gross myocardial infarction, and valvular deformities; the latter for atherosclerosis. The heart was then separated from the aorta, washed, dried with absorbent paper, and weighed. Sections of the myocardium near its base and the aorta were cut, fixed in 10% formalin for 24 hours and then stained with orcein for elastic tissue and hematoxylin-eosin. Frozen sections were cut and stained with Sudan III for fat. These sections were then carefully examined microscopically. To rule out the possibility of co-existent systemic arterial hypertension or aortic valvular deformity, arterial blood pressure curves were obtained with the Hamilton[10] technique at fast camera speeds on 4 rabbits of Group C anesthetized with nembutal, 25 mg./kg. intravenously; and these curves were compared with similar records obtained under identical conditions on 7 normal rabbits of Series A.

Results. The heart weights of all the animals are assembled in Table 1. It will be seen from this table that the heart weight in the control Group A varied from 1.9 to 5.8 gm., and only 2 hearts weighed more than 5 gm.; average heart weight in this group, 3.8 gm. A similar range and average was found in control Group B; the heart weight ranging from 2.1 to 6.6 gm., and only one heart weighed more than 5 gm.; average heart weight, 3.9 gm. The heart weights of the remaining 16 rabbits constituting experimental Group C were greater: they ranged from 3.8 to 11.2 gm. and 12 hearts weighed more than 5 gm.; average heart weight, 6.3 gm. It is thus apparent that atherosclerosis resulted in cardiac hypertrophy. This is shown more clearly in the distribution curve (Fig. 11), in which the number of cases in each range of actual heart weight is plotted in each of the three series of animals.

When the degree of gross atherosclerosis was correlated with the degree of microscopic coronary artery involvement, a rough parallel-

* Supplied through the kindness of Parke, Davis & Co.

ism was found in the majority of instances. Furthermore, a rough correlation could be obtained between the degree of microscopic coronary atheromatosis and heart weight; namely, the greater the coronary involvement the heavier the heart, although exceptions were noted. To rule out the possibility that the differences in heart weight might be due to differences in body weight, the distribution

TABLE 1.—HEART WEIGHTS OF ALL RABBITS.

Rabbit No.	Heart weight (gm.).	Necropsy body weight (gm.).	Days on diet.
Control Untreated Group A.			
1	4.9	2160	0
2	4.4	2160	0
3	5.2	2160	0
4	5.8	2160	0
5	4.2	1640	0
6	4.2	1700	0
7	4.0	1600	0
8	4.1	1820	0
9	4.0	1820	0
10	4.5	1860	0
11	3.6	1400	11
12	2.2	1250	7
13	3.9	1125	1
14	2.8	990	7
15	3.6	1220	1
16	2.9	975	7
17	1.9	500	5
18	2.1	675	4
Control Treated Group B.			
19	3.3	1125	26
20	3.5	1050	51
21	4.8	950	68
22	3.6	1200	25
23	2.1	860	52
24	6.6	1350	78
Experimental Group C.			
25	5.2	1050	47
26	3.9	825	85
27	4.8	1200	120
28	6.7	1550	119
29	7.7	1475	119
30	5.8	1600	120
31	7.0	2100	120
32	5.9	1050	86
33	6.3	820	84
34	5.0	1320	67
35	4.0	1000	69
36	5.5	1240	90
37	9.5	1820	90
38	8.0	2000	90
39	11.2	1550	90
40	3.8	1200	42

of the animals according to the ratio of the heart weight to body weight was analyzed as a distribution curve in the three series (Fig. 12). This figure definitely shows that the rabbits in experimental Group C had heart weight-body weight ratios well outside

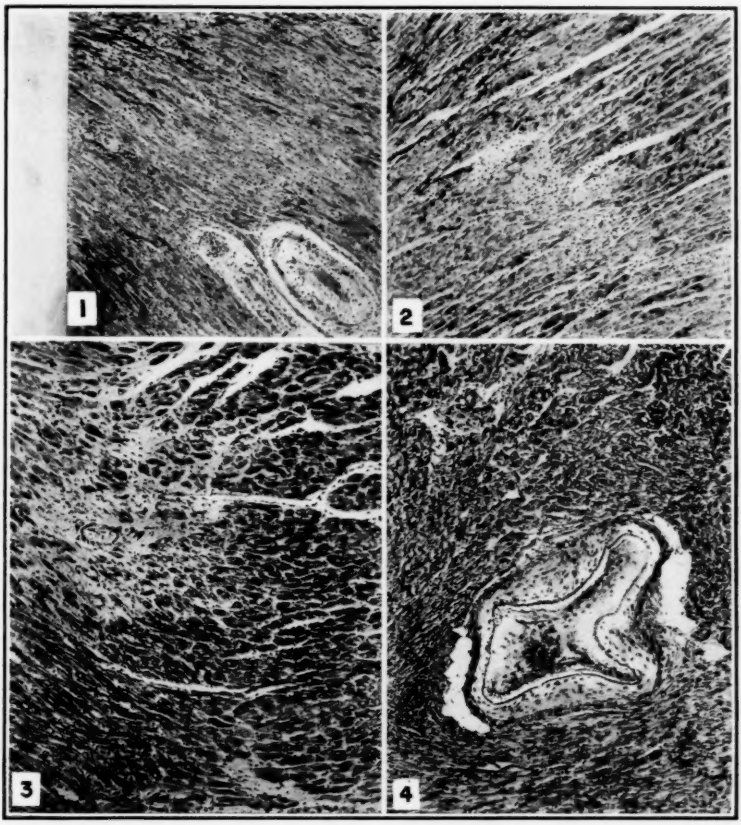

FIG. 1.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—24×), showing a branch of the coronary artery with marked intimal proliferation.

FIG. 2.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—24×), showing an extensive area of myocardial fibrosis.

FIG. 3.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—40×), showing an extensive area of myocardial fibrosis and prominent vacuolization of the myocardial fibers.

FIG. 4.—Myocardium of a rabbit of Group C (Orcein, and iron-hematoxylin stain—36×), showing prominence of the internal elastic lamina and marked intimal and subintimal proliferation of the coronary artery

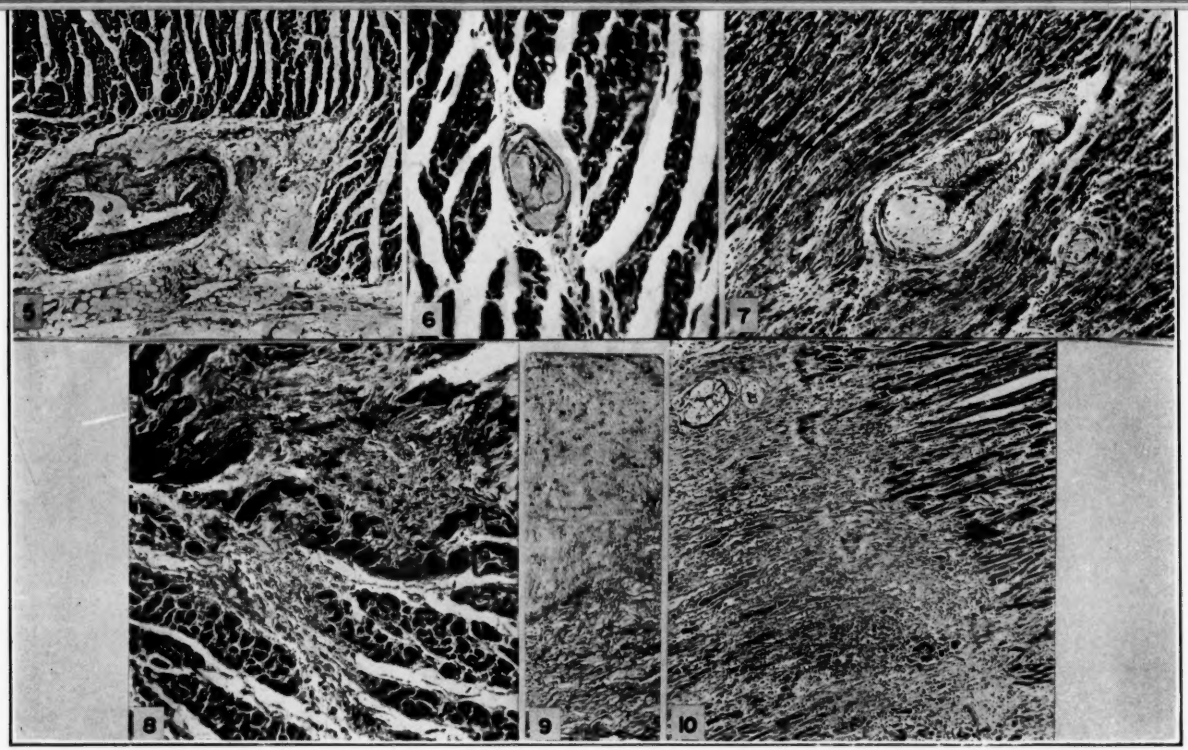

FIG. 5.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—14×), showing a localized fatty degeneration of the large branch of the coronary artery.

FIG. 6.—Myocardium of a rabbit of Group C (H. and E.—35×), showing a marked fatty proliferation of the intima with fatty degeneration and severe constriction of the lumen of a small branch of the coronary artery.

FIG. 7.—Myocardium of a rabbit of Group C (Weigert's iron, H. and E.—25×), showing a marked fatty intimal proliferation and fairly severe constriction of the lumen of a moderate sized branch of the coronary artery.

FIG. 8.—Myocardium of a rabbit of Group C (H. and E.—47×), showing an early myocardial infarction in the fibrotic region and absence of striations and nuclei of the muscle fibers in the upper portion of the photograph.

FIG. 9.—Myocardium of a rabbit of Group C (H. and E.—19×) showing an old myocardial infarct rather sharply demarcated from relatively normal myocardium.

FIG. 10.—Myocardium of a rabbit of Group C (H. and E.—19×), showing an early organizing myocardial infarct with absence of muscle fibers and replacement by early connective tissue. The lumen of the small artery in this region is almost completely obliterated.

the limits of the animals in control Groups A and B, clearly indicating that the hypertrophy of the heart was not due to differences in body weight.

Microscopically, the lesions observed were similar to those described by other investigators,[2,13] and in the early stages consisted of the appearance of large pale cells filled with a lipoid material in the form of fine and coarse droplets. This initial lipoidosis was observed in an intimal and subintimal location. In more advanced stages the lipoid infiltration occasionally passed into the media and adventitia resulting in an apparent fragmentation of the internal elastic lamina. In some regions intimal and subintimal lipoidosis was so marked as to cause marked encroachment or almost complete obliteration of the arterial lumen (Figs. 1, 4, 6, 7, 10). Generally

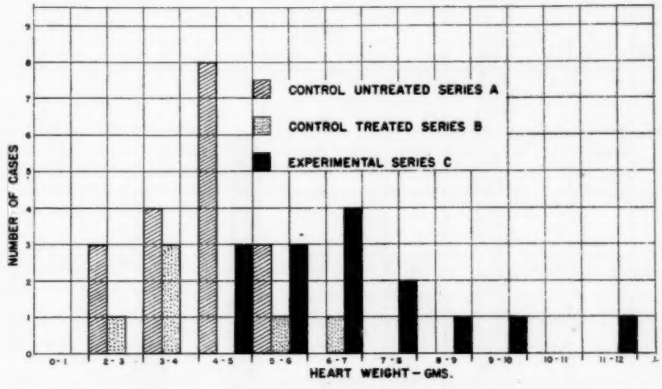

FIG. 11.—Distribution of the actual heart weights in the three series of rabbits. Note the heavier heart weights of those rabbits which developed atheromatosis (Series C).

it was the smaller coronary arteries which presented the most marked encroachment on their lumina, although the larger coronary vessels also presented the characteristic sub-endothelial lipoid infiltration histologically (Fig. 4). Not infrequently the subendothelial changes were patchy and plaque-like in nature presenting a picture rather characteristic of early human coronary sclerosis (Fig. 5). In addition striking changes were evident in the myocardium. These consisted of: 1, large areas where cross-striations could not be identified and pyknosis to complete absence of nuclei was noted (Fig. 8); 2, other areas where moderate to marked fatty degeneration was evident; 3, regions where increased amounts of interstitial connective tissue and patchy areas of myocardial fibrosis were present (Figs. 2 and 3); and 4, most striking of all, areas where very recent, acute organizing, and old myocardial infarcts were seen (Figs. 8, 9, and 10).

FIG. 10.—Myocardium of a rabbit of Group C (H. and E.—19×), showing an early organizing myocardial infarct with absence of muscle fibers and replacement by early connective tissue. The lumen of the small artery in this region is almost completely obliterated.

Discussion. Atherosclerosis of the aorta can be eliminated as a factor in the cardiac hypertrophy in our experiments, since it has been shown by Fahr, *et al.*[8] that the energy consumption of the heart and the external work of the left ventricle is not increased

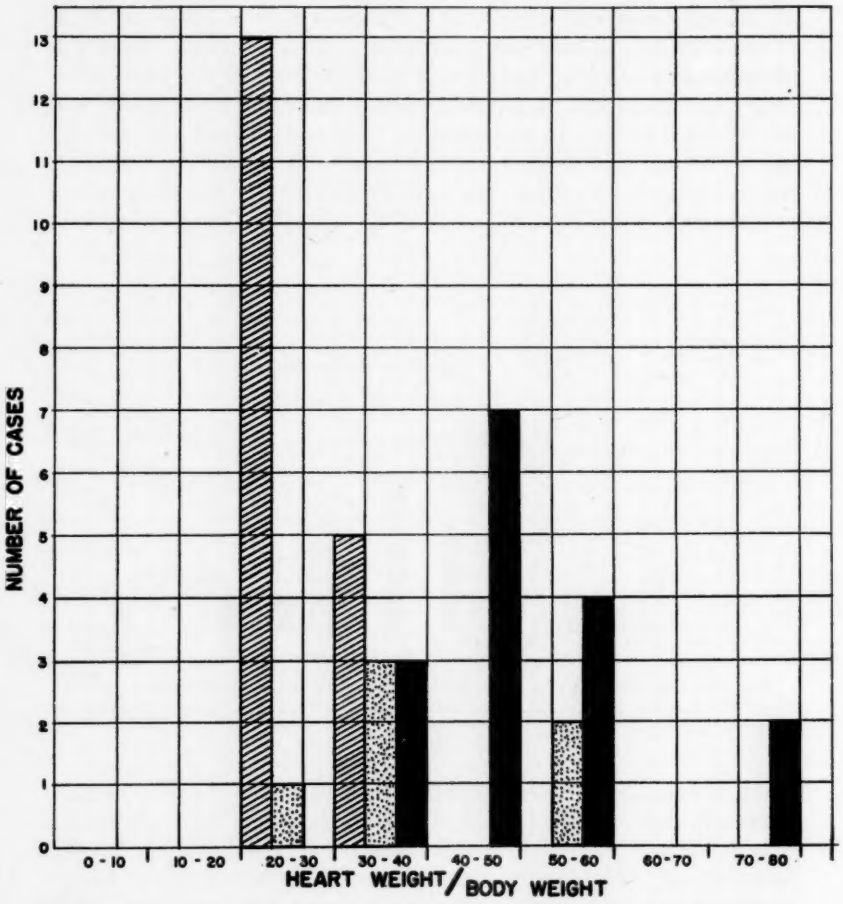

FIG. 12.—Distribution of the heart weight/body weight ratios in the three series of rabbits. The body weight used was that at the time of necropsy. Conventions as in Figure 11. Note the relatively heavier hearts of the rabbits which developed atheromatosis (Series C).

when the coefficient of volume elasticity of the large arteries is increased. Aortic valvular deformity, both stenosis and incompetence, can be eliminated, since normal pulse wave contours were obtained (*cf.* Fig. 13, *A* and *B*). Systemic arterial hypertension can also be excluded as an etiologic agent, since direct blood pressure

determinations showed the pressure to be in the normotensive range (*cf.* Fig. 13, *A* and *B*, and Table 2). Actually the blood pressure values fell in the range recently found to exist in the normal unanes-

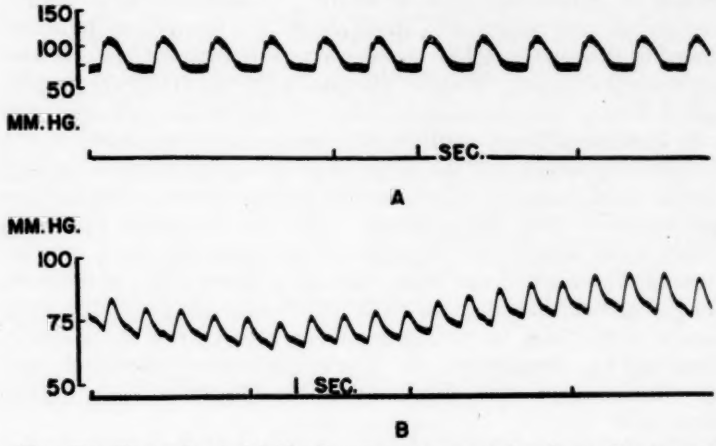

FIG. 13.—Femoral arterial blood pressure curves taken by a direct puncture (Hamilton technique) in a normal rabbit (*A*) and in one which developed atheromatosis (*B*) to show the similarity in contour and pressure levels. Ordinates show mm. of Hg; abscissæ, time in sec. Note the respiratory variation in blood pressure in B.

thetized rabbit.[22] There is therefore no reason to assume an absolute increase in the work of the heart as a result of hypertension, although the ischemia following coronary atheromatosis might be expected to lead to a relative increase in heart work even in the absence of

TABLE 2.—SYSTEMIC ARTERIAL BLOOD PRESSURE PRIOR TO SACRIFICE OF ANIMAL.

	Systolic pressure, mm. Hg.	Diastolic pressure, mm. Hg.
Untreated Control Group A.		
1	105	75
2	125	80
3	115	75
4	100	65
5	115	75
6	85	60
7	90	75
Experimental Group C.		
28	120	80
29	95	75
30	90–75	80–60
31	115	85

hypertension. It might be conceived that the increase in heart weight resulted from a fatty infiltration of the myocardium. Microscopic examination indicated, however, that when fatty changes occurred, they were in the nature of a secondary degenerative rather than a primary infiltrative phenomenon. Furthermore the possi-

bility of hypertrophy that might result from a vitamin B deficiency was avoided by mixing adequate amounts of brewer's yeast or a vitamin B concentrate with the diet, and histologically there was no evidence of a beri-beri type of heart. In addition, if a dietary factor *per se* were responsible, there should not have been the sharp distinction in heart weights between control treated Group B and experimental Group C. Finally, the possibility that the hypertrophy resulted from myocarditis, acute, subacute or chronic, was excluded by the absence of these conditions on microscopic examination.

It is thus apparent that the ischemia of the myocardium secondary to the induced coronary atheromatosis was the cause of the cardiac hypertrophy in our experiments. The exact modus operandi, whether it be through initial cardiac dilatation, through a relative increase in the work of the heart, through a direct effect of ischemia upon the myocardial fibers or their metabolism, or through a combination of all these factors, is not dealt with by our experiments.

Summary and Conclusions. 1. The relationship of cardiac hypertrophy to coronary sclerosis was made the subject of direct experimental study.

2. For this purpose 22 rabbits were fed on a high cholesterin diet with the addition of the vitamin B complex. Sixteen of these rabbits subsequently developed moderate to severe atherosclerosis including involvement of the coronary arteries. The resulting heart weights of these were compared with 18 rabbits serving as untreated controls and with 6 rabbits, which although on the special diet, failed to develop gross or microscopic evidence of coronary or aortic atherosclerosis. All the rabbits were in the same age group with comparable body weights and the comparisons are therefore valid.

3. It was found that of the 16 rabbits developing atherosclerosis 12 showed heart weights of more than 5 gm. with an average cardiac weight of 6.3 gm.; whereas the 18 control untreated rabbits showed an average heart weight of 3.8 gm., with only 2 hearts weighing more than 5 gm.; while in the 6 remaining rabbits on the special diet but which did not develop atherosclerosis, only 1 heart weighed more than 5 gm., and the average heart weight was 3.9 gm.

4. To rule out factors other than the atheromatosis, direct systemic arterial blood pressures and pulse wave contours were obtained, and histologic sections carefully studied.

5. Evidence is presented to exclude atherosclerosis of the aorta, systemic arterial hypertension, aortic valvular defects, inflammatory disease of the myocardium and other actions of the diet as factors in the production of cardiac hypertrophy in our experiments.

6. It is therefore concluded that coronary atherosclerosis *per se* produces cardiac hypertrophy in the rabbit. Ischemia of the heart appears to be involved in some way in the mechanism.

We are indebted to Mr. J. Ransohoff for his technical assistance, and to Dr. O. Saphir, of the Department of Pathology, for his kindness in checking these microscopic interpretations.

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METHIONINE AND CYSTINE, SPECIFIC PROTEIN FACTORS PREVENTING CHLOROFORM LIVER INJURY IN PROTEIN-DEPLETED DOGS.

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The experiments listed below show clearly that methionine and to a less extent cystine prevent the liver necrosis of chloroform poisoning in the protein-depleted dog. Protein-depleted dogs may be fatally poisoned (with extreme liver necrosis) by 15 to 20 minutes of light surgical chloroform anesthesia. Given a few grams of methionine 24 to 4 hours before the chloroform anesthesia, the same depleted dog will show no evidence of frank intoxication or signs of liver injury following 40 minutes of chloroform anesthesia (Tables 3, 4 and 5). This is truly a remarkable protective reaction and deserves careful study and analysis. This reaction may give the answer to the puzzling question, How does chloroform cause hyaline liver necrosis?

In a recent report[13] from this laboratory it was demonstrated that liver injury due to chloroform anesthesia in the dog increases

in extent as the body protein stores are depleted. It was shown that a single large protein feeding protected a protein-depleted dog from injury by an otherwise fatal chloroform anesthesia. It was also shown that large amounts of the simple amino-acid glycine before anesthesia failed to confer any protection.

The importance of protein was recognized by Goldschmidt, Vars and Ravdin,[7] when as a result of their dietary studies on rats, they concluded that "A high protein diet previous to the anesthesia with chloroform reduces the incidence of hepatic cellular necrosis, even in livers with a high lipid content . . . ."

An interesting observation is recorded in the early experiments of Howland and Richards.[8] They described a marked increase in the neutral sulphur fraction of the urinary sulphur in dogs following chloroform anesthesia of 2 to 5 hours' duration. Since that time numerous investigators have demonstrated the biologic detoxication of a number of aromatic organic compounds by conjugation with cystine and elimination as mercapturic acids in the neutral sulphur fraction of the urine. Stekol's[16b] demonstration of the detoxication of benzylchloride in the dog, rabbit, and rat to form S-benzyl-mercapturic acid indicates that detoxication by cysteine (or cystine) is not necessarily confined to strictly aromatic organic compounds.

Methods. All dogs used in these experiments were active healthy adults. As indicated in detail in the individual protocols, the dogs' reserve stores of protein were depleted by maintenance on a low protein diet consisting of cane sugar 71%, lard 15.1%, protein-free butter 7.2%, bone ash 1.8%, salt mixture[6] 1.8%, cod-liver oil 3%. Liver or lean beef 10 to 15 gm., yeast powder 1 gm., thiamine 150 I. U. and nicotinic acid 25 mg. were added as described in the individual protocols. The details of amounts and routes of administration of the amino-acid supplements are included in the individual protocols. When given intravenously the amino-acids were dissolved in saline containing 2 to 10 gm. glucose. At the beginning of the experiments the dogs' plasma protein levels were normal (6 to 6.5 gm. per 100 cc. with a few exceptions). The constant drain on body protein stores extending over a period of 4 to 14 weeks finally resulted in a lowered plasma protein level. A plasma protein level of 4 to 5 gm. per 100 cc. for at least 1 week before administration of the chloroform anesthesia was assumed to indicate a rather severe depletion of reserve protein stores.[11]

Blood samples were drawn from the external jugular vein with 1.4% sodium oxalate used as anticoagulant. Plasma protein determinations were carried out by the macro-Kjeldahl method on the oxalated plasma without correcting for non-protein nitrogen, fibrinogen was determined by micro-Kjeldahl, and icterus index by comparison of the oxalated plasma with standards prepared according to the method of Farahaugh and Medes.[5]

The dogs were given no food but water *ad libitum* 24 hours before the administration of the chloroform.

Anesthesia was induced with ether and then chloroform was given by the drop method. A light surgical anesthesia was maintained. All dogs recovered from the anesthesia quite rapidly and were conscious within 2 to 4 minutes.

Experimental Observations. In general terms we may say that a loss of appetite for a day or so may be due to ether anesthesia alone. When we observe that the icterus index rises and the fibrinogen content of the plasma falls after chloroform anesthesia, we feel confident from the study of large numbers of animals with autopsy examination of the liver, that there will be found some liver injury. The degree of injury will parallel closely the fall in the fibrinogen levels. On the contrary, after chloroform anesthesia when we find no icterus and no fall in the fibrinogen and a dog clinically undisturbed, we may safely assume absence of chloroform liver necrosis.

TABLE 1.—PROTEIN, CYSTINE, AND METHIONINE PROTECT AGAINST CHLOROFORM POISONING.

Dog No.	Low-protein diet, weeks.	Preliminary treatment.	Duration of anesthesia, min.	Plasma protein level, mg. per 100 cc.	Fibrinogen.		Clinical condition.
					Before chloroform, mg. per 100 cc.	48 hrs. after chloroform, mg. per 100 cc.	
39–20	9	None	20	5.17	373	63*	Dead 40 hours
39–16	6	Lean beef	20	4.6–5.3	...	...	Normal
38–299	6	Lean beef	20	4.5–5.3	...	...	Normal
38–241	8	Plasma protein	20	5.2–6.3	...	352	Slight intox.
38–241	15	Plasma protein	20	4.7	370	205	Slight intox.
39–16	7	l-cystine	25	4.2	177	129	Slight intox.
38–169	6	l-cystine	27	5.0	235	260	Normal
38–340	12	l-cystine	30	5.0	223	160*	Moderate intox.
38–340	15	l-cystine	40	5.2	351	648	Dead 4 days
38–338	6	l-cystine	20	4.7	355	195	Slight intox.
38–338	13	l-cystine	40	4.6	237	166	Dead 4 days
39–157	9	dl-methionine	40	4.9	450	421	Normal
39–157	13	None	15	4.8	327	38*	Dead 36 hours
39–12	6	dl-methionine	40	4.5	264	222	Normal
39–12	10	None	15	4.5	347	44	Dead 47 hours
39–164	4	dl-methionine	40	4.2	332	401	Normal
39–164	7	Amino acids†	20	3.9	368	50	Severe intox.
39–130	11	dl-methionine	40	5.3	478	419	Normal
39–130	14	Amino acids‡	20	4.8	375	165*	Dead 40 hours
39–10	7	None	10	5.1	387	130	Moderate intox.
39–10	10	dl-methionine	40	5.1	402	343	Slight intox.

* Twenty-four hours after chloroform.
† l-tyrosine, l-histidine, l-alanine, l-glutamic acid.
‡ l-tryptophane, dl-phenylalanine, dl-isoleucine, l-aspartic acid, l-valine, dl-lysine.

Table 1 shows three groups of experiments in summary. The first group of 5 experiments gives further evidence that meat protein by mouth or plasma protein by vein within 24 hours before chloroform anesthesia will give more or less protection against the chloroform liver injury. The second group of 6 experiments shows that cystine given in various amounts and periods before the chloroform

anesthesia does confer some protection against the chloroform liver injury. The picture may be confused because cystine in the doses given to plasma-depleted dogs may in itself cause some icterus and fatty changes in the liver cells.

The third group of 10 experiments shows that methionine has a remarkable protective action where given 4 to 24 hours before the chloroform anesthesia. In fact these protein-depleted dogs given methionine will tolerate twice the lethal chloroform anesthesia and give little or no evidence of liver injury and minimal or no clinical disturbance. Other amino-acids confer no protection.

Experiment 1 shows that nicotinic acid and lecithin added to the dogs' diet do not protect against chloroform injury. Dog 39–20 (Exp. 1) showed a typical fatal response 36 hours after 20 minutes of chloroform anesthesia. The histologic finding of 80% to 90% hyaline central necrosis was identical with that seen in the livers of dogs not receiving nicotinic acid or lecithin. This is in accord with the results of both Goldschmidt, Vars and Ravdin[7] and Barrett, Best, MacLean and Ridout,[1] who showed that choline did not materially affect the incidence or extent of liver damage from chloroform or carbon tetrachloride, respectively.

Experiments 2 and 3 (Dogs 39–16 and 38–299) show that a single large protein feeding (lean beef) can completely prevent liver injury from 20 minutes of chloroform anesthesia in the protein-depleted dog. These experiments are entirely in agreement with a similar experiment described in our previous report.[13]

Experiments 4 and 5 were both carried out on the same animal (Dog 38–241). In both experiments plasma protein given by vein afforded considerable but not absolute protection. As measured by clinical condition, icterus index, and drop in blood fibrinogen, the injury produced by the second anesthesia (Exp. 5) was somewhat more severe. In Experiment 4, it is interesting to note how rapidly the plasma protein level falls after the initial sudden rise following the plasma injection.

Clinical Histories. *Experiment 1, Dog 39–20, adult male poodle.*

Oct. 2 to 5. Fasted. Weight at end of fast 6.2 kilos. Plasma protein level 5.95 gm. per 100 cc. Red cell hematocrit 51%.

Oct. 6 to Dec. 2. Fed daily 135 gm. of low protein diet with supplement of 10 gm. beef, 25 mg. nicotinic acid, and 150 I. U. thiamine daily. Ate an average of 80% to 90% daily. Plasma protein level, Nov. 16, 4.68 gm. per 100 cc. Weight 4.3 kilos. Dec. 3, ate 60% diet.

Dec. 4. Ate 5 gm. lecithin with 50% of diet.

Dec. 5. Ate 5 gm. lecithin with 90% of diet.

Dec. 6. Ate about 50% of diet containing 10 gm. lecithin.

Dec. 7. Fasted. Weight 4.2 kilos.

Dec. 8. Red cell hematocrit 41%. Plasma protein level 5.2 gm. per 100 cc. Fibrinogen 373 mg. per 100 cc. *Chloroform anesthesia 20 minutes.* Ate very little of food offered.

Dec. 9. Dog very ill. Icterus index 18. Fibrinogen 63 mg. per 100 cc. Semicomatose at 6 P.M.

Dec. 10. Dog found dead. *Autopsy* revealed a friable liver with lobules showing conspicuous central congestion. Microscopically, there was practically complete disappearance of normal liver tissue with about 80% to 90% central hyaline necrosis.

Experiment 2, Dog 39–16, female Spitz.

Aug. 5. Weight 7.3 kilos. Started daily low protein diet of 135 gm. with 5 gm. fresh pork liver, 1 gm. yeast powder and 150 I. U. thiamine. Eaten 100% unless otherwise stated. Plasma protein level 6.24 gm. per 100 cc.

Sept. 5. Plasma protein level 5.03 gm. per 100 cc.

Sept. 18. Plasma protein level 4.58 gm. per 100 cc. Weight 7.2 kilos.

Sept. 23. Ate 1 pound of lean beef.

Sept. 24. Fasted.

Sept. 25. Plasma protein level 5.28 gm. per 100 cc.—rise due to meat feeding. *Chloroform anesthesia 20 minutes.* Ate only 20% of diet in P.M.

Sept. 26. Dog in good condition, bright and lively. Ate 80% of diet. Plasma shows no jaundice.

Sept. 27. Dog in excellent condition. Ate 100% diet.

Sept. 28. Dog normal. Returned to kennels (see Exp. 6 below).

Experiment 3, Dog 38–299, female bull mongrel.

Aug. 2. Plasma protein level 5.67 gm. per 100 cc. Started daily low protein diet of 135 gm. plus daily supplement of 1 gm. yeast powder, 150 I. U. thiamine and 5 gm. fresh pork liver. Weight 8.2 kilos. Diet eaten 100% unless otherwise stated.

Aug. 23. Plasma protein level 4.97 gm. per 100 cc.

Sept. 11. Plasma protein level 4.90 gm. per 100 cc.

Sept. 18. Plasma protein level 4.49 gm. per 100 cc. Weight 8 kilos.

Sept. 19. Ate 460 gm. lean beef.

Sept. 20. Fasted. Weight 8.2 kilos.

Sept. 21. Plasma protein level 5.28 gm. per 100 cc.—note rise due to meat feeding. *Chloroform anesthesia 20 minutes.* Ate regular diet fed 2 hours after anesthesia.

Sept. 22. Plasma protein level 5.18 gm. per 100 cc. Plasma shows no jaundice. Ate 60% of diet. Dog in very good condition.

Sept. 23. Dog normal. Ate 100% diet. Sept. 25, returned to kennels.

Experiment 4, Dog. 38–241, adult female hound mongrel.

Aug. 6. Placed on low protein diet, 165 gm., plus 5 gm. fresh pork liver, 1 gm. yeast powder and 150 I. U. thiamine daily. Plasma protein level 6.74 gm. per 100 cc. Weight 12.2 kilos.

Sept. 11. Plasma protein level 4.89 gm. per 100 cc. Weight 11.3 kilos.

Sept. 18. Plasma protein level 5.03 gm. per 100 cc. Weight 11.3 kilos.

Sept. 28. Plasma protein level 5.17 gm. per 100 cc. In 2 intravenous injections received a total of 270 cc. of citrated plasma containing a total of 16.4 gm. of plasma protein. Weight 10.4 kilos.

Sept. 29. Fasted.

Sept. 30. Plasma protein level 6.30 gm. per 100 cc.—note rise due to plasma injections. *Chloroform anesthesia 20 minutes.* Ate 100% diet in P.M.

Oct. 1. Plasma protein level 6 gm. per 100 cc. Icterus index 7. Appears slightly ill but is moderately active. Ate about 65% of diet.

Oct. 2. Dog still somewhat ill, but active. Icterus index 8. Ate about 75% of diet.

Oct. 3. Plasma protein level 5.33 gm. per 100 cc. Fibrinogen 349 mg. per 100 cc. Icterus index 9. Ate about 50% of diet.

Oct. 4. Condition much better. Icterus index 5. Ate about 50% of diet.

Oct. 5. Dog normal. Weight 10.5 kilos—low protein diet continues.

Experiment 5, Dog 38–241, continued from Experiment 4.

Oct. 16. Plasma protein level 4.81 gm. per 100 cc. Liver supplement to daily diet increased to 15 gm. Weight 10 kilos.

Oct. 27. Replaced liver supplement with equal amount of beef daily.

Nov. 16. Plasma protein level 4.67 gm. per 100 cc.

Nov. 22. Plasma protein level 4.71 gm. per 100 cc. Since Nov. 2 has eaten only an average of 40% to 50% of diet. Received intravenously 140 cc. of citrated plasma containing 8.4 gm. of plasma protein.

Nov. 23. Received intravenously 220 cc. of citrated plasma containing 13 gm. of plasma protein. Fasted.

Nov. 24. *Chloroform anesthesia 20 minutes.* Fibrinogen 373 mg. per 100 cc. Diet practically untouched in P.M.

Nov. 25. Condition good; fed about 60% of diet by stomach tube. Icterus index 13. Fibrinogen 316 mg. per 100 cc. Slight intoxication.

Nov. 26. Condition good. Refuses diet. Plasma protein level 5.96 gm. per 100 cc. Fibrinogen 205 gm. per 100 cc. Icterus index 17.

Nov. 27. Ate about 40% of diet. Condition good. Nov. 28, ate about 60% of diet.

Nov. 29. Fibrinogen 205 mg. per 100 cc. Icterus index 3. Condition normal. Weight 8.2 kilos. Returned to kennels.

TABLE 2.—CYSTINE PROTECTS AGAINST CHLOROFORM POISONING.

Hours before or after chloroform.	Plasma protein, gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinical condition.
Experiment 6.	(*Dog 39–16.*)	*Low-protein diet for 11 weeks.*			
0	4.24	177	1	Fast	Normal
(25 minutes chloroform anesthesia preceded by cystine supplements for 12 days.)					
24	4.15	157	8	0	Slight intoxication
48	..	129	9	10	Good
72	..	123	5	15	Very good
120	3.70	168	1	70	Normal
Experiment 7.	(*Dog 38–169.*)	*Low-protein diet for 6 weeks.*			
0	5.00	235	6	Fast	Normal
(27 minutes chloroform anesthesia preceded by cystine supplements for 4 days.)					
24	5.14	330	5	100	Normal
48	5.14	260	2	100	Normal
72	..	217	2	100	Normal
96	..	221	1	100	Normal
120	5.02	278	1	100	Normal

Experiments 6, 7 (Table 2), 8, and 10 indicate that *cystine* supplements to the low protein diet (and in some instances cysteine intravenously) protected the protein-depleted dogs from the effects of chloroform anesthesias which were sufficiently prolonged to be fatal in unprotected animals. In connection with the use of cystine as a specific protective agent, it was noted that cystine supplements greater than a few grams would often cause jaundice with a considerable icterus index before anesthesia. It is known that under certain conditions of low or incomplete protein intake cystine will cause a

considerable increase in liver fat.[17] Just how this fatty change in the liver could cause jaundice in the protein-depleted dog we do not know, but it suggests impaired liver function. (In several normal dogs with adequate protein intake not included in this report, equally large doses of cystine failed to cause jaundice.) Despite the fact that jaundice was present in a number of these dogs (Exps. 6, 7, and 9) before anesthesia, these animals survived a lethal chloroform anesthesia. On the basis of clinical condition and decrease in blood fibrinogen, liver injury was not very severe in any of these experiments.

Experiments 9 and 11 were done on dogs previously protected by cystine from doses of chloroform which would have been fatal to unprotected animals. In Experiments 9 and 11 Dogs 38–340 and 38–338, given 40 minutes of chloroform anesthesia (twice the lethal dose) died on the fourth day after anesthesia, but these experiments are complicated by factors which probably favored the chloroform liver injury. As a result of the cystine administration both dogs had considerable jaundice before the anesthesia was given. In Dog 38–340 there were large abscesses at the site of each subcutaneous injection of cystine and a considerable amount of cystine remained unabsorbed. Dog 38–338 was fasted for 48 hours instead of 24 hours before the anesthesia which would render the dog still more susceptible to chloroform poisoning. Despite these facts microscopic examination of the livers of both dogs revealed only a very occasional necrotic liver cell, although the hepatic parenchyma showed extensive fatty change. This is in striking contrast to the very extensive hyaline central necrosis seen in the livers of protein-depleted dogs which died as a result of only 15 to 20 minutes of chloroform anesthesia.

Clinical Histories. *Experiment 6, Dog 39–16, continued from Experiment 2 (Table 2).* Diet is same as in Experiment 2, plus daily supplement of 10 gm. beef instead of liver.

Nov. 16. Plasma protein level 5.03 gm. per 100 cc. Weight 7.5 kilos.
Nov. 22 and 23. Ate only 50% daily diet plus 2 gm. cystine.
Nov. 24 to 26. Ate only 35% of diet daily plus 2 gm. cystine.
Nov. 27 to 29. Ate 30% of diet daily.
Nov. 30. Fed 70% of diet by stomach tube plus 2 gm. cystine.
Dec. 1 and 2. Beef supplement increased to 15 gm. but ate 50% of diet daily plus 2 gm. cystine.
Dec. 3 and 4. Ate 50% of diet daily plus 5 gm. cystine.
Dec. 5. Diet plus 3 gm. cystine fed by stomach tube in two portions.
Dec. 6. Fasted. Weight 7 kilos.
Dec. 7 to 12. See Table 2.

Experiment 7, Dog 38–169, adult male bull dog (Table 2).

Oct. 9. Placed on low protein diet, 165 gm. daily with 1 gm. yeast powder and 10 gm. beef.
Oct. 14. Started daily supplement of 25 mg. of nicotinic acid and 150 I. U. of thiamine. Weight 8.5 kilos.
Oct. 16. Plasma protein 6.10 gm. per 100 cc. Oct. 30, plasma protein 4.79 gm. per 100 cc.

Nov. 15. Daily diet supplemented with 2 gm. cystine.
Nov. 16. Daily diet supplemented with 4 gm. cystine. Plasma protein 5 gm. per 100 cc.
Nov. 17. Daily diet supplemented with 6 gm. cystine.
Nov. 18. Daily diet supplemented with 10 gm. cystine. Fibrinogen 235 mg. per 100 cc. Icterus index 0.
Nov. 19. Fasted. Weight 7.7 kilos.
Nov. 20 to 26. See Table 2.

Experiment 8, Dog 38–340, adult female Spitz.
Oct. 5. Plasma protein, 5.94 gm. per 100 cc. Weight 9.3 kilos.
Oct. 6. Placed on low protein diet, 165 gm. daily with 1 gm. yeast powder and 15 gm. meat.
Oct. 14. Started daily supplement of 25 mg. nicotinic acid and 150 I. U. thiamine. Weight 9.3 kilos.
Oct. 15 to Nov. 6. Ate an average of 85% to 90% of diet daily. Plasma protein 5.21 gm. per 100 cc. (Nov. 6).
Nov. 7 to Dec. 13. Ate an average of 65% to 75% of diet. Plasma protein 4.78 gm. per 100 cc. Fibrinogen 269 mg. per 100 cc. (Dec. 13).
Dec. 14. Ate 3 gm. of cystine with 60% of diet.
Dec. 15 to 17. Ate about 35% of diet daily plus a total of 3 gm. cystine.
Dec. 18. Plasma protein 4.89 gm. per 100 cc. Fibrinogen 234 mg. per 100 cc.
Dec. 19 to 24. Ate an average of 40% of diet plus 6 gm. of cystine.
Dec. 25. Fasted. Fibrinogen 201 mg. per 100 cc. Icterus index 0. Weight 8.8 kilos.
Dec. 26. Plasma protein 5 gm. per 100 cc. Fibrinogen 223 mg. per 100 cc. Icterus index 0+. About 5 hours before anesthesia gave 1.45 gm. of cysteine plus 5 gm. glucose in 150 cc. of physiologic saline by vein. *Chloroform anesthesia 30 minutes.* Ate no food in P.M.
Dec. 27. Condition good. Fairly active. Fibrinogen 160 mg. per 100 cc. Icterus index 8.
Dec. 28. Condition good. Ate 15% of food. Icterus index 11.
Dec. 29. Condition better. Ate 30% of food. Fibrinogen 285 mg. per 100 cc. Icterus index 6.
Dec. 30 and 31. Condition normal. Ate 50% of food each day. On Dec. 31, fibrinogen 324 mg. per 100 cc. Icterus index 3.

Experiment 9, Dog 38–340, continued from Experiment 8.
Jan. 3 to Jan. 14. Ate an average of 50% of diet (same as in Exp. 8). Weight, Jan. 14, 8.3 kilos.
Jan. 15. Plasma protein 4.94 gm. per 100 cc. Ate about 30% of diet.
Jan. 16. Ate about 30% of diet, rest given by stomach tube. An undetermined amount was vomited.
Jan. 17. Fasted. At 9 P.M. 5 gm. of cystine almost completely dissolved in 10% sodium carbonate was given subcutaneously.
Jan. 18. Dog somewhat ill. Severe local reaction at sites of injection. At 10 A.M. received 5 gm. cystine plus 5 gm. glucose by stomach tube of which one-fifth was vomited. Plasma protein 5.20 gm. per 100 cc. Fibrinogen 351 mg. per 100 cc. Icterus index 1. *Chloroform anesthesia 40 minutes.* Food untouched in P.M.
Jan. 19. Has vomited considerable mucus during night. Fibrinogen 574 mg. per 100 cc. Icterus index 7. Intravenous glucose 25 gm. in 100 cc. of saline. Vomiting continues.
Jan. 20. Although obviously weakened, still active and conscious. Vomiting mucus has continued through the night. Fibrinogen 648 mg. per 100 cc. (due to abscesses). Icterus index 30. Intravenous glucose 20 gm. in 125 cc. of saline and later 20 gm. in 175 cc. of saline. Vomiting continues.

Jan. 21. Condition worse. Semicomatose late in evening despite several doses of intravenous glucose. Fibrinogen 526 mg. per 100 cc. Icterus index 26.

Jan. 22. Found dead. On autopsy found two large abscesses at sites of cystine injections. Liver grossly yellowish in color. Microscopically, only a very occasional liver cell is necrotic, but the liver cells show extensive fatty change and definite icterus with brown casts in many bile canaliculi. This is not the typical picture of delayed chloroform poisoning.

Experiment 10, Dog 38–338, male hound mongrel.

Oct. 2 to 4. Fasted.

Oct. 5. Started low protein diet 165 gm. Supplemented daily with 25 mg. nicotinic acid, 150 I. U. thiamine and 10 gm. meat. Weight 12.2 kilos.

Oct. 16. Plasma protein 5.31 gm. per 100 cc.

Oct. 31. Plasma protein 4.88 gm. per 100 cc.

Nov. 3 and 9. Ate 50% of diet.

Nov. 11. Diet containing 10 gm. cystine untouched.

Nov. 12. Fasted except for 10 gm. cystine, 4 gm. Klim, 5 gm. glucose given by stomach tube.

Nov. 13. Repeated above mixture at 11 A.M. Plasma protein 4.68 gm. per 100 cc. Fibrinogen 355 mg. per 100 cc. Icterus index 14. *Chloroform anesthesia 20 minutes* at 3 P.M. Ate practically none of diet in P.M.

Nov. 14. Vomited mucus once. Condition fairly good. Fibrinogen 283 mg. per 100 cc. Icterus index 26. Ate practically none of diet.

Nov. 15. Condition good and fairly active but ate none of diet. Given 25 gm. glucose in 100 cc. saline by vein. Plasma protein 4.25 gm. per 100 cc. Fibrinogen 195 mg. per 100 cc. Icterus index 27.

Nov. 16. Condition good, but ate very little of diet. Fibrinogen 135 mg. per 100 cc. Icterus index 18.

Nov. 17. Condition good. Fed 50% of diet by tube; ate rest by following day. Fibrinogen 184 mg. per 100 cc. Icterus index 7.

Nov. 18. Condition normal. Ate 70% of diet. Fibrinogen 238 mg. per 100 cc. Icterus index 1.

Nov. 19. Returned to kennels. Weight 10.6 kilos.

Experiment 11, Dog 38–338, continued from Experiment 10.

Dec. 15 to 25. Ate an average of 65% of low protein diet, supplemented with 5 gm. lecithin and increased beef to 15 gm. daily. Weight (Dec. 15) 10.2 kilos.

Dec. 26 and 27. Ate 50% of diet daily containing 6 gm. of cystine.

Dec. 28 to 30. Ate about 25% of diet daily, containing about 4 gm. of cystine.

Dec. 31. Ate only about 10% of diet containing 0.2 gm. cystine. Icterus index 6. Jan. 1, fasted.

Jan. 2. Plasma protein 4.55 gm. per 100 cc. Fibrinogen 237 mg. per 100 cc. Icterus index 5. About 4 hours before anesthesia received intravenously a solution of 2.3 gm. cysteine hydrochloride, 1.5 gm. sodium bicarbonate and 5 gm. glucose in 150 cc. of physiologic saline. This caused dog to vomit thick mucus repeatedly for about 1 hour. *Chloroform anesthesia 40 minutes.* Ate no food in P.M.

Jan. 3. Condition fairly good. Fibrinogen 232 mg. per 100 cc. Icterus index 10. Ate no food.

Jan. 4. Obviously ill. Fibrinogen 166 mg. per 100 cc. Icterus index 11. Received 150 cc. of saline subcutaneously. Vomited mucus. Ate no food.

Jan. 5. Condition poor but still active. Received 100 cc. saline by vein and 100 cc. saline intravenously in the morning and 200 cc. saline subcutaneously in the afternoon because of intermittent vomiting. Con-

dition worse later in the day. Fibrinogen 185 mg. per 100 cc. Icterus index 14. Ate no food.

Jan. 6. Semicomatose. Plasma protein 4.27 gm. per 100 cc. Fibrinogen 185 mg. per 100 cc. Icterus index 19. Dead at 9.30 A.M. On autopsy liver was grossly saffron yellow in color and central areas of lobules only slightly accentuated. Microscopically, the liver cells in the mid-zone especially show extreme fatty degeneration. There are many pigmented phagocytes in the center of the liver lobules. Icterus is not obvious. No typical hyaline liver necrosis noted.

It is believed that *methionine* can replace cystine in any reaction of detoxication and methionine is definitely lipotropic in contrast to cystine which in certain conditions favors the deposit of fat in the liver. Therefore one might suspect that methionine would be superior to cystine as an agent protective against chloroform liver injury. In these experiments it is obvious that methionine is distinctly more effective.

Clinical Histories. *Experiment 12, Dog 39–157, adult female Spitz (Table 3).*

Jan. 12. Placed on low protein diet, 165 gm. with daily supplement of 15 gm. beef, 25 mg. nicotinic acid, 150 I. U. thiamine and 5 gm. lecithin. Weight 7.5 kilos.

Jan. 15. Plasma protein 6.87 gm. per 100 cc.

Jan. 16 to Feb. 14. Ate 100% of diet. Plasma protein (Feb. 3) 5.09 gm. per 100 cc.

Feb. 15 to Mar. 10. Ate an average of 80% of diet daily.

Mar. 11. Ate about 50% of diet containing a supplement of 2 gm. methionine. Rest fed by stomach tube with an additional 2 gm. methionine. Small amount vomited.

Mar. 12. Plasma protein 4.96 gm. per 100 cc. Ate 15% of diet. Fed rest with 2 gm. methionine by stomach tube. Some vomited.

Mar. 13. Fasted. Weight 7.9 kilos.

Mar. 14 to Mar. 18. Glucose 10 gm. in 100 cc. saline intravenously on 15, 16 and 17 (see Table 3).

Experiment 13, Dog 39–157, continued from Experiment 12 (Table 3).

Mar. 19 to Apr. 9. Ate a daily average of about 55% of same diet as in Exp. 12 with lecithin replaced by 200 mg. choline hydrochloride daily.

Apr. 10. Fasted. Weight 7.5 kilos.

Apr. 11 and 12. See Table 3.

Apr. 13. Found dead. On autopsy, the liver was uniformly reddish brown with centers of lobules markedly congested. Microscopically, there was extensive hyaline central necrosis involving about 60% to 70% of the lobule cross-section.

Table 3 shows 2 experiments which are convincing. The same protein-depleted dog given methionine by mouth and by vein before the anesthesia tolerated 40 minutes chloroform anesthesia and showed no evidence of liver injury and little or no clinical disturbance. After an interval of 4 weeks the dog was given chloroform anesthesia for 15 minutes (no methionine) which caused a typical fatal chloroform poisoning in 36 hours.

TABLE 3.—METHIONINE PROTECTS AGAINST CHLOROFORM POISONING.

Hours before or after chloroform.	Plasma protein, gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinical condition.
Experiment 12 (Dog 39–157). Low-protein diet for 8 weeks.					
0	4.96	450	0	Fast	Normal
(Chloroform anesthesia—40 minutes, preceded by methionine in diet, 2 gm. per day, for 2 days and by vein, 2 gm., 3 hours before anesthesia.)					
24	4.95	383	0	5	Good
48	4.94	421	0	5	Good
72	..	453	0	5	Good
96	..	448	0	5	Normal
120	..	438	0	40	Normal
Experiment 13 (Dog 39–157). Low protein diet continued 4 weeks more. No methionine given.					
2	4.83	327	0	Fast	Normal
(Chloroform anesthesia—15 minutes.)					
24	4.76	38	12	0	Intoxicated
36	Death—chloroform poisoning.			Extensive liver injury.	

Clinical Histories. *Experiment 14, Dog 39–12, adult female hound mongrel.*

Jan. 23. Placed on diet (165 gm. daily), supplemented daily with 10 gm. beef, 25 mg. nicotinic acid, 200 mg. choline hydrochloride, 150 I. U. of thiamine chloride. Plasma protein 5.90 gm. per 100 cc. Weight 11.1 kilos.

Feb. 27. Plasma protein 4.78 gm. per 100 cc. Weight 11.1 kilos.

Mar. 5 and 6. Supplemented diet with 2 gm. methionine each day.

Mar. 7. Fasted except for 2 gm. of methionine plus 3 gm. glucose given by stomach tube.

Mar. 8. Before anesthesia, plasma protein 4.45 gm. per 100 cc. Fibrinogen 264 mg. per 100 cc. Icterus index 0. One hour before *40 minutes of chloroform anesthesia* the dog was given 2 gm. methionine plus 3 gm. glucose by stomach tube. Fed 100% of diet plus 1 gm. methionine by stomach tube in P.M.

Mar. 9. Condition good although dog appears slightly ill. Fed about 75% of diet by stomach tube. Fibrinogen 314 mg. per 100 cc. Icterus index 0.

Mar. 10. Condition good. Ate 100% of diet. Fibrinogen 222 mg. per 100 cc. Icterus index 1.

Mar. 11. Condition normal. Ate 100% of diet. Plasma protein 4.22 gm. per 100 cc. Fibrinogen 181 mg. per 100 cc. Icterus index 0.

Mar. 12. Condition normal. Plasma protein 4.49 gm. per 100 cc. Fibrinogen 223 mg. per 100 cc. Icterus index 0.

Experiment 15, Dog 39–12, continued from Experiment 14.

Mar. 13 to Apr. 7. Continued to eat 100% of low protein diet of Exp. 14.

Apr. 8. Fasted. Weight 11.6 kilos.

Apr. 9. Plasma protein 4.47 gm. per 100 cc. Fibrinogen 347 mg. per 100 cc. Icterus index 0. *Chloroform anesthesia 15 minutes.* Shortly after recovery, ate 100% of regular diet.

Apr. 10. Obviously ill and inactive. Vomited bile-stained mucus several times. Plasma protein 4.29 gm. per 100 cc. Fibrinogen 58 mg. per 100 cc. Icterus index 9. Received 250 cc. of 5% glucose in saline subcutaneously.

Apr. 11. Dead at 11 A.M. Shortly before death, fibrinogen 44 mg. per 100 cc. Icterus index 21. At autopsy the liver lobules grossly showed deep red central areas. Microscopically, there was extensive central hyaline necrosis corresponding to about 50% to 60% of the lobule cross-sectional areas.

Experiments 14 and 15 are very like those in Table 3. Again, methionine given by stomach tube on several days before the chloroform anesthesia protects the dog against 40 minutes of chloroform and the dog shows no evidence of liver injury and only slight clinical intoxication. After an interval of 4 weeks the dog was given 15 minutes of chloroform anesthesia (no methionine) which caused a fatal chloroform poisoning in 48 hours.

Clinical Histories. *Experiment 16, Dog 39–164, adult female Boston bull* (Table 4).

Mar. 26 to 31. Fasted.

Apr. 1. Placed on low protein diet, 165 gm. daily with daily supplements of 15 gm. beef, 150 I. U. of thiamine, 25 mg. nicotinic acid, 200 mg. choline hydrochloride. Weight 8.3 kilos. Plasma protein 5.56 gm. per 100 cc.

Apr. 2 to 22. Ate 100% of diet. Plasma protein (April 17) 4.31 gm. per 100 cc.

Apr. 23 and 24. Received diet supplement of 2 gm. methionine each day.

Apr. 25. Fasted. Weight 8.4 kilos.

Apr. 26 to 29. Received 2 gm. methionine with food on April 26 (see Table 4).

Experiment 17, Dog 39–164, continued from Experiment 16 (Table 4).

May 1 to 13. Ate an average of 80% of diet as given in Experiment 16. Weight (May 13) 6.8 kilos.

May 14. Fasted except for amino acids supplement: 1 gm. l-tyrosine, 1 gm. l-alanine, 1 gm. l-histidine hydrochloride, 1 gm. l-glutamic acid and 5 gm. glucose in 100 cc. of saline by stomach tube.

May 15. Repeated amino-acid mixture by stomach tube at 9 A.M. Plasma protein 3.92 gm. per 100 cc. Fibrinogen 368 mg. per 100 cc. Icterus index 0. *Chloroform anesthesia 20 minutes* at noon. Ate 100% of diet. Some vomited later.

May 16. Condition fairly good. Plasma protein 4.27 gm. per 100 cc. Fibrinogen 310 mg. per 100 cc. Icterus index 8. Refused food. At 8 P.M. condition poor, conjunctiva extremely congested. Fibrinogen 156 mg. per 100 cc. Icterus index 13. Received 10 gm. glucose in 100 cc. saline. Ate no food.

May 17. Condition very poor. Very weak. Chemosis and congestion of conjunctiva. Hemorrhage anterior chambers of both eyes. Slow oozing of blood from previously inconspicuous sores on both front legs. Fibrinogen 50 mg. per 100 cc. Icterus index 15. Ate no food. Almost fatal intoxication and bleeding.

May 18. Condition poor, but appears brighter. Very weak. Improved after receiving intravenously 15 gm. glucose in 100 cc. saline. Fibrinogen 109 mg. per 100 cc. Icterus index 25. Ate no food.

May 19. Slightly improved. Extreme weakness somewhat relieved by 15 gm. glucose in 100 cc. saline given intravenously. Fibrinogen 168 mg. per 100 cc. Icterus index 22. Ate no food.

May 20. Condition much better. Still weak, but ate some of diet. Plasma protein 3.55 gm. per 100 cc. Fibrinogen 197 mg. per 100 cc. Icterus index 7.

May 21. Condition much better. Ate about 50% of food.

May 22. Condition normal. Fibrinogen 275 mg. per 100 cc. Icterus index 1. Returned to kennels.

Table 4 shows again the powerful protective action of methionine and in contrast the neutral effect of a group of non-sulphur containing

amino-acids. The dog when given methionine by mouth and by vein before the anesthesia tolerates 40 minutes of chloroform anesthesia with little or no clinical disturbance and no signs of liver injury. After 3 weeks the dog is given a mixture of amino-acids as control for the methionine and 20 minutes chloroform anesthesia. This caused a very severe liver injury with high icterus index and very low fibrinogen levels. The dog was severely intoxicated and bled from skin ulcers and into the chambers of both eyes. It appeared certain that death would follow but recovery took place within a week.

TABLE 4.—METHIONINE PROTECTS AGAINST CHLOROFORM POISONING. TYROSINE, ALANINE, HISTIDINE AND GLUTAMIC ACID DO NOT PROTECT.

Hours before or after chloroform.	Plasma protein, gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinica condition.
Experiment 16 (Dog 39–164). Low-protein diet for 4 weeks.					
0	4.23	332	0	Fast	Normal
(Chloroform anesthesia—40 minutes, preceded by methionine, 2 gm. in diet for each of 2 days, and by vein, 2 gm. shortly before anesthesia.)					
24	4.44	352	1	100	Good
48	4.56	401	1	35	Good
72	4.45	479	0	30	Normal
96	..	..	0	50	Normal
Experiment 17 (Dog 39–164). Low-protein diet continued for 3 weeks.					
0	3.92	368	0	Fast	Normal
(Chloroform anesthesia—20 minutes, preceded by tyrosine, alanine, histidine, and glutamic acid given 24 and 3 hours before anesthesia.)					
24	4.27	310	8	100	Intoxication
48	..	50	15	0	Severe intoxication
72	..	109	25	0	Poor
96	3.63	168	22	0	Improved
120	3.55	..	7	0	Fairly good

Clinical Histories. *Experiment 18, Dog 39–130, adult male mongrel (Table 5) (like Table 4).*

Jan. 15. Placed on low protein diet (same as Dog 39-164, Exps. 16 and 17). Plasma protein 7.23 gm. per 100 cc. Weight 13.5 kilos.

Feb. 27. Plasma protein 5.40 gm. per 100 cc. Weight 12.4 kilos.

Apr. 17. Plasma protein 5.09 gm. per 100 cc. Weight 11.8 kilos.

Apr. 29. Ate 40% of diet. Apr. 30, fasted.

May 1 to 4. See Table 5.

May 6. Condition normal. Plasma protein 5.40 gm. per 100 cc. Fibrinogen 425 mg. per 100 cc. Icterus index 0. Ate 50% of diet. Weight 11.3 kilos.

Experiment 19, Dog 39–130, continued from Experiment 18 (Table 5).

May 7 to 22. Ate a daily average of 50% to 60% of same diet used in Exp. 18.

May 23. Fasted except for amino-acid mixture of 1 gm. l-tryptophane, 1 gm. dl-phenylalanine, 1 gm. dl-isoleucine, 1 gm. l-aspartic acid, 1 gm. l-valine, 1 gm. dl-lysine dihydrochloride, and 5 gm. glucose in 100 cc. saline, given by stomach tube at 4 P.M.

May 24. Gave above amino-acid mixture by stomach tube at 9.45 A.M. Plasma protein 4.80 gm. per 100 cc. Fibrinogen 375 mg. per 100 cc. Icterus

index 0. *Chloroform anesthesia 20 minutes* at 1 P.M. Ate about 10% of diet in P.M. Vomited once during night.

May 25. Inactive and ill but bright. At 9 A.M. fibrinogen 188 mg. per 100 cc. Icterus index 7. At 1 P.M. fibrinogen 165 mg. per 100 cc. Icterus index 9. Ate no food.

May 26. Found dead. Vomited several times during night. Icterus index approximately 15 (blood taken at autopsy). Autopsy revealed a grossly yellowish brown liver with reddish hemorrhagic central areas standing out. Microscopically, there was extensive central hyaline necrosis corresponding to 70% to 80% of the lobules in cross-section.

TABLE 5.—METHIONINE PROTECTS AGAINST CHLOROFORM POISONING. TRYPTOPHANE, PHENYLALANINE, ISOLEUCINE, ASPARTIC ACID, VALINE AND LYSINE DO NOT PROTECT.

Hours before or after chloroform.	Plasma protein, gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinical condition.
Experiment 18 (Dog 39–130). Low-protein diet for 11 weeks.					
0	5.39	478	0	Fast	Normal
(Chloroform anesthesia—40 minutes, preceded by methionine intravenously, 2.5 gm. 5 hours before and 2.3 gm. 2 hours before.)					
24	5.35	440	0	60	Good
48	5.21	419	0	15	Good
72	5.19	403	0	85	Normal
120	5.40	425	0	50	Normal
Experiment 19 (Dog 39–130). Low-protein diet continued for 3 weeks.					
0	4.80	375	0	Fast	Normal
(Chloroform anesthesia—20 minutes, preceded by amino acid mixture 21 hours and 4 hours before, by stomach tube.)					
24	..	165	9	10	Intoxicated
44	Death—chloroform poisoning.				

Table 5 shows that a total of 4.8 gm. methionine given intravenously 5 and 2 hours before anesthesia will give complete protection against 40 minutes of chloroform anesthesia. The control again shows that non-sulphur containing amino-acids confer no protection and fatal chloroform poisoning follows 20 minutes anesthesia.

Clinical Histories. *Experiment 20, Dog 39–10, adult female shepherd mongrel (Table 6),*

Jan. 29. Started diet. Identical with that of Dog 39–12 in Exp. 15. Plasma protein 6.60 gm. per 100 cc. Weight 8.9 kilos.

Jan. 30 to Mar. 12. Ate an average of 90% of diet. Plasma protein (Mar. 12) 5.40 gm. per 100 cc. Weight 9 kilos.

Mar. 13 to Apr. 16. Ate 50% to 60% of diet.

Apr. 17. Plasma protein 5.22 gm. per 100 cc. Weight 9.1 kilos.

Apr. 18. Fasted.

Apr. 19 to 23. See Table 6.

Experiment 21, Dog 39–10, continued from Experiment 20 (Table 6).

Apr. 24 to May 9. Ate an average of 50% of diet.

May 10 to 14. See Table 6.

May 15. Condition normal. Returned to kennels. Weight 9.1 kilos.

Table 6 shows a reversal of the sequence to control some factors related to repeated insults and liver cell regeneration as shown by

MacNider.[10] The first chloroform injury to the protein-depleted dog is caused by only 10 minutes anesthesia (about one-half to two-thirds the lethal exposure). This caused definite intoxication and evidence of some liver injury. After an interval of 3 weeks, which is adequate for liver repair, the dog was given methionine intravenously 20 and 2 hours before anesthesia. Chloroform anesthesia of 40 minutes then caused not the slightest clinical disturbance and no signs of liver injury. This is evidence again that methionine confers a strong resistance against chloroform liver injury.

TABLE 6.—METHIONINE PROTECTS AGAINST CHLOROFORM POISONING.

Hours before or after chloroform.	Plasma protein, gm. per 100 cc.	Fibrinogen, mg. per 100 cc.	Icterus index.	Food consumed, %.	Clinical condition.
Experiment 20 (Dog 39–10). Low-protein diet for 7 weeks.					
0	5.05	387	0	Fast	Normal
(Chloroform anesthesia—10 minutes. No methionine.)					
24	4.84	177	1.5	50	Slight intoxication
48	..	130	4	20	Slight intoxication
72	4.60	164	1	30	Good
96	..	205	0	50	Very good
Experiment 21 (Dog 39–10). Low-protein diet for additional 3 weeks.					
0	5.12	402	0	Fast	Normal
(Chloroform anesthesia—40 minutes, preceded by 5 gm. methionine intravenously in two portions, 20 and 2 hours before chloroform.)					
24	5.00	377	1	0	Excellent
48	..	343	0	25	Excellent
72	..	321	0	50	Excellent
96	..	...	...	50	Normal

Discussion. Perfect experiments in physiology or pathology are rare indeed and when encountered deserve comment. The experiments in Table 5 approach this goal of perfection. We note that this protein-depleted dog given methionine by vein 5 and 2 hours before chloroform anesthesia tolerated 40 minutes (twice the lethal period) and showed no evidence of liver injury or clinical intoxication. After an interval of 3 weeks a mixture of amino-acids (other than methionine or cystine) were given as controls before anesthesia. In this experiment 20 minutes caused a fatal chloroform poisoning with death in 44 hours and the typical picture of massive central liver necrosis. Table 6 is almost as satisfactory and shows the primary injury due to 10 minutes chloroform. After 3 weeks the dog was given methionine and subjected to 4 times the anesthesia period (40 minutes) which caused no clinical disturbance and no signs of liver injury.

Two perennial questions invariably arise in any discussion of chloroform poisoning. What mechanism accounts for the liver cell necrosis and why is the liver necrosis or injury (fat) produced by chloroform and other organic halogenated compounds invariably centrally located? Many inadequate answers to these questions

will be found in the literature and our readers may not agree that our answer to these questions is correct or even approximately so, yet we submit a thesis which is in harmony with the experiments given above.

We suggest that protein protects animals from the toxic effects of chloroform anesthesia by making available methionine and cystine. Both casein, which was found so effective[7] in protecting rats, and beef muscle and plasma protein used by us, are good sources of methionine or cystine. The evidence strongly suggests that these amino-acids are concerned with the specific detoxication of chloroform to form a conjugation product similar to the mercapturic acids already described in the literature. (In preliminary experiments, methods which have resulted in the isolation of known mercapturic acids have thus far failed to yield any compound which might be a similar detoxication product for chloroform.) Thus it is suggested that protein-depleted dogs are very susceptible to liver injury by chloroform as a direct consequence of the relatively limited amount of methionine- and cystine-containing liver protein. Briefly put, for the chloroform experiment the protein-depleted dog is probably a cystine- and methionine-depleted dog.

An alternative but to us a less attractive theory would attribute to methionine and (or) cystine a key rôle in the construction of new liver protein or reconstruction of damaged liver cell protein. Moreover it will be recalled that experiments[11] with plasma-depleted dogs give evidence that cystine and methionine are almost key amino-acids when it comes to the production of much new plasma protein. This, however, does not prove that these two amino-acids are key acids for the building of new liver protein. It is difficult to visualize this extensive production of new liver protein containing much of the methionine given 3 to 5 hours before the chloroform anesthesia, although one perhaps could imagine these S-amino-acid groups being incorporated in large protein molecules in a very short time.

The results of the above experiments show that methionine is much more effective than cystine. Although both amino-acids can be converted to mercapturic acids to equivalent degrees, it is conceivable that the amounts of cystine (and cysteine) given caused a considerable increase in liver fat, especially since these animals may not have been getting adequate choline. The observations of Tucker and Eckstein,[17] Beeston and Channon[2] and others certainly indicate that cystine can cause relatively large increases in liver fat which might impair liver function to some extent. Certainly the jaundice in most of the cystine-fed animals is an indication of some disturbance in liver function. In spite of this confusing reaction, it is significant that cystine was unquestionably of protective value.

As a control we have tested a variety of amino-acids (see Tables 4 and 5) under identical conditions. Alone (glycine) or in various combinations, the non-sulphur amino-acids seem to be inert and confer no protection against chloroform poisoning.

It is well known that the function of a number of enzymes as well as glutathione is intimately associated with the presence of –SH groups. It is also known that certain halogenated compounds conjugate very readily with –SH groups[12,15] and thus completely eliminate their ability to function (for example, in an oxidation-reduction system). Binet, Weller and Gondard[3] have described a decrease in the glutathione content of the liver following chloroform given *per os*. Other workers[9] have shown that feeding cysteine increases the liver glutathione content. It is conceivable that injury or necrosis of liver cells may result from more or less extensive conjugation of chloroform with –SH groups of glutathione and vital enzyme systems. Where the number of such inactivated groups per cell is relatively small (large reserve protein stores, or short anesthesia, or increased cysteine available), then liver cell injury will be prevented.

Just exactly what happens to cystine or methionine when administered to a protein-depleted animal on a low protein diet we are unprepared to say. Nielsen, Gerber and Corley[14] have demonstrated the retention in the dog of the nitrogen of a cystine supplement to a low protein diet, and Stekol[16a] has shown that l-cystine and dl-methionine sulphur is retained under similar conditions. It is possible that the liver of the protein-depleted dog retains a relatively large amount of these amino-acids by increasing the S-amino-acid content of liver protein already present, by increasing the glutathione content, or in some other way. In any case the S-containing amino-acid would become rapidly available for conjugation purposes since (in Exp. 18, Dog 39–130, Table 5) methionine was given only 5 hours before 40 minutes of chloroform anesthesia and no perceptible liver injury was shown. Experiments are now in progress to demonstrate to what extent sulphur-containing amino-acids are incorporated by or retained in liver tissue following the feeding of cystine or methionine to protein-depleted animals on a low protein diet.

If the action of chloroform and certain other organic compounds on the liver can be interpreted in terms of specific conjugation with and inhibition of free –SH groups, then one might suspect that the fatty change and necrosis most commonly seen as a result of the action of these materials is central because of the relatively lower oxygen tensions at the centers of the liver lobules. Furthermore, the work of Blalock and Mason[4] indicates that in contrast to venous blood from other organs, venous blood from the liver contains considerably less oxygen. With this rapid fall in oxygen tension within the liver lobule and concomitant fall in oxidation reduction potential,

it is logical to assume that the number of free sulphydryl groups would increase and disulphide groups decrease from the periphery to the center of the liver lobule: hence central cell necrosis. In this connection it is interesting to note that Goldschmidt, Ravdin and Lucké[6] observed a decrease in the extent of liver damage when the chloroform used for anesthesia was volatilized with oxygen.

No adequate explanation has ever been given to indicate why chloroform has a specific affinity for liver cells rather than for other gland cells rich in ferments (for example the pancreas) nor have we any explanation to offer.

Summary. Methionine and to a less extent cystine given by mouth or by vein 24 to 5 hours before anesthesia give a remarkable and almost complete protection to the protein-depleted dog against chloroform poisoning.

Other non-sulphur-containing amino-acids alone or in various combinations as tested convey no protection against chloroform poisoning in similar experiments.

A single large beef feeding or plasma protein by vein 24 to 48 hours before anesthesia will likewise protect against chloroform poisoning and it is suggested that the sulphur-containing amino-acids are responsible.

The protein-depleted dog will succumb to 15 to 20 minutes light chloroform anesthesia and show extensive liver necrosis. The dog protected by methionine will tolerate 40 minutes chloroform anesthesia with little or no clinical disturbance and no evidence of liver injury.

It is suggested that the sulphydryl groups combine with chloroform. This combination may inactivate enzyme systems and thus bring about cell death unless there is an adequate reserve of cystine and methionine.

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CLINICAL STUDIES OF EXPERIMENTAL HUMAN VITAMIN B COMPLEX DEFICIENCY.

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Claims have recently been made for the efficacy of members of the vitamin B complex in a variety of clinical conditions. Many of them are based on uncontrolled observations, and their validity is therefore difficult to assess. It is our belief that only when the environment has been carefully controlled and coëxisting deficiencies eliminated can a reliable estimate be made of the rôle of vitamin B factors in clinical medicine. In accordance with this belief one of us in 1933[3a] studied the changes which took place in a healthy volunteer who for approximately 1 year consumed a diet deficient only in the vitamin B complex. This experiment enabled us to describe clinical signs and alterations in function attributable to vitamin B complex deficiency. An extension of these observations seemed desirable and, because group experiments in this field are relatively unsatisfactory due to the unusual coöperation required of the subjects, it was decided to use the same volunteer and to repeat the experiment in its essentials, employing more detailed methods of study and testing the effects of components of the vitamin B complex unknown in 1933. The present report therefore deals with the results of repeated clinical examinations and of studies of cardiovascular, neurologic and hematopoietic functions and of alterations in the Roentgen appearance of the gastro-intestinal tract made while the subject consumed the deficient diet alone and also following the addition to the diet of thiamin, of riboflavin and of brewer's yeast. The studies made at this time on fluid balance, body weight, nitrogen excretion, carbohydrate metabolism and response to insulin have been reported elsewhere.[4]

Methods. The study was made in the metabolic ward of the Hospital of the University of Pennsylvania from February 25 to June 25, 1938. During that time the subject, a healthy woman aged 60, voluntarily consumed a constant daily quantity of a weighed diet. As described elsewhere[4] the diet

was adequate in protein, fat, carbohydrate and total calories and was supplemented with optimal amounts of vitamins A, C and D and of iron and calcium. Thiamin was present in approximately one-third the individual's minimal requirement as calculated by the Cowgill formula.[1] It was assumed that other members of the vitamin B complex were correspondingly reduced. Daily fluid intake was constant. The experiment was divided into five consecutive periods: 1, the first week on the deficient diet which was regarded as the control period; 2, the subsequent 8 weeks during which time signs of deficiency developed; 3, a period of 18 days when thiamin hydrochloride* alone was added to the diet in doses ranging from 20 to 120 mg. daily; 4, 20 days during which riboflavin, 6 mg. daily, was administered in addition to thiamin; 5, a final 18 days when brewer's yeast† alone, 42 gm. daily, was given. This period was shorter than desired, due to unavoidable circumstances, so that the effects of this therapeutic agent were evident but probably not maximal before it was necessary for the subject to leave the hospital.

The subject was examined daily and a record kept of symptoms and physical signs. Pulse and blood pressure readings were made 3 times daily under basal conditions. Electrocardiograms and orthodiagrams were made at the beginning and end of each period. Roentgen examination of the gastrointestinal tract was made at the end of each period. Following administration of a standard barium meal to the fasting subject, observations were carried out at hourly intervals for 4 to 5 hours. Neurologic examination and determination of electrical irritability of the peripheral nerves, according to the method previously described,[6] were made at the end of each period. The following studies of the blood were made frequently: erythrocyte counts in triplicate, using pipettes certified by the U. S. Bureau of Standards; hematocrit determinations in triplicate, using Wintrobe tubes, and estimations of hemoglobin percentage by the Sahli method. Mean corpuscular volume and mean corpuscular hemoglobin were calculated in the usual fashion.[13] Morphologic changes in the blood were observed from smears prepared with Wright's stain.

Results. 1. Cardiovascular Studies. After 5 weeks on the experimental diet, the subject complained of dyspnea and palpitation (Table 1). She also experienced sharp pain in the left anterior chest from time to time. Occasionally it occurred during exertion, but its location and character were not typically anginal.

On physical examination short periods of tachycardia were observed which lasted a few hours. Later they became more frequent, until, during the last 5 days of deficiency, the resting pulse rate was never below 90 and frequently was as high as 108. The average of 100 (Fig. 1) represented an increase of 17 beats per minute over the control period. With the patient at rest the pulse varied abruptly both in rate and strength. At times a soft systolic murmur was audible over the aortic area. No significant changes in resting blood pressure, electrocardiogram or orthodiagram were observed.‡

All the cardiovascular symptoms and physical signs regressed

* This material (as Betabion) and riboflavin were supplied through the courtesy of Merck & Co.

† The brewer's yeast was kindly supplied by Dr. L. J. Harris of the Harris Laboratories, Tuckahoe, N. Y., as "Brewer's Yeast-Harris Medicinal Powder."

‡ We are indebted to Dr. F. C. Wood for the electrocardiograms and orthodiagrams and for their interpretations.

promptly after the administration of thiamin. At the end of 1 week the average resting pulse was 90, by the end of the second week it was normal and remained so thereafter. Variation in intensity of the pulse was not again observed nor was the aortic murmur heard. Dyspnea and precordial distress disappeared.

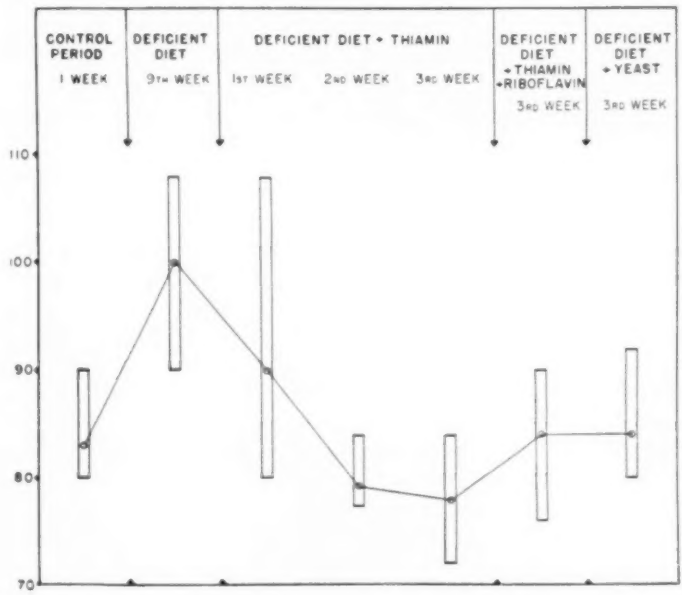

FIG. 1.—Changes in the resting pulse rate. Columns indicate the maximum variations in each period.

TABLE 1.—CLINICAL OBSERVATIONS ON A VITAMIN B DEFICIENT DIET.

Clinical observations.	Vitamin B deficient diet.			Deficient diet + thiamin.	Deficient diet + thiamin, + riboflavin.	Deficient diet + yeast.
	1st week.	5th week.	9th week.			
Symptoms:						
Easy fatigue	0	++	++++	+	++	0
Anorexia	+	+++	++++	+	++	+
Cardiac	0	+	+++	0	0	0
Gastro-intestinal	0	++	+++	+++	+++	0
Neurologic	0	+	++	0	0	0
Mental	0	+	++++	++	++	0
Physical signs and special observations:						
Change in appearance	0	+	++++	++	++	0
Edema	+	++	++	++	++	+
Increased pulse rate	0	+	++	0	0	0
G.I. Roentgen changes	0	..	++	++	++	0
Neurologic signs	0	+	++	0	0	0
Blood changes	0	0	+	++	++	+++

These findings are in some respects contrary to recent reports. Changes in the electrocardiogram believed to be characteristic of vitamin B deficiency have been reported by several observers.[2,12a,b] But since these observations were not controlled, it is impossible to estimate the rôle of unknown factors. Jolliffe and his coworkers[5] recently reported electrocardiographic changes in human thiamin deficiency. It has been observed in animals[8] that deficiency of several factors of the B complex alters the manifestations of a single deficiency, so that the difference in results may represent a difference between the manifestations of thiamin deficiency alone compared to that of the entire B complex in the human.

2. Gastro-intestinal Studies. Mild anorexia was present after 1 week on the diet (Table 1) and ultimately became extreme. Other gastro-intestinal symptoms were heartburn, a constant sense of epigastric fullness, abdominal distention and constipation. Mild soreness of the tongue was an occasional complaint. Toward the end of deficiency nausea and vomiting were frequent, and during the last few days there was moderately severe generalized abdominal pain.

Appetite returned promptly following the administration of thiamin. Within 48 hours aversion to food was less extreme and by the end of 1 week a mild sensation of hunger was experienced. This return of appetite was not associated with any change in the other gastro-intestinal symptoms, except that the abdominal pain disappeared. Toward the end of the second week of thiamin therapy appetite again decreased and, in spite of the continued administration of thiamin and the addition of riboflavin, did not again return toward normal until yeast was given.

Roentgen examination of the gastro-intestinal tract (Table 2, Fig. 2) at the end of deficiency showed no abnormality except some increased calibre of the jejunal loops. After the subject had received thiamin for 18 days there was delayed gastric emptying and slight delay in small bowel motility. Increased calibre of the jejunal loops was still evident. Riboflavin did not significantly alter these findings. Following the administration of yeast, however, there was marked improvement in the small intestinal motility, the head of the barium column having reached the hepatic flexure 4 hours and 40 minutes after the ingestion of the barium, while under thiamin and riboflavin therapy a comparable film was not observed until 6 hours from the start of the examination. A slight delay in gastric emptying persisted. At no time were segmented and dilated loops of small bowel observed as described by Pendergrass and Comroe,[9] Mackie and Pound,[7] and Snell and Camp.[11]

3. Neurologic Studies. Three days after beginning the experimental diet diminution in electrical irritability of the peripheral nerves and some disturbance of sensation were observed (Table 3). A steady decrease in electrical irritability and exaggeration of the

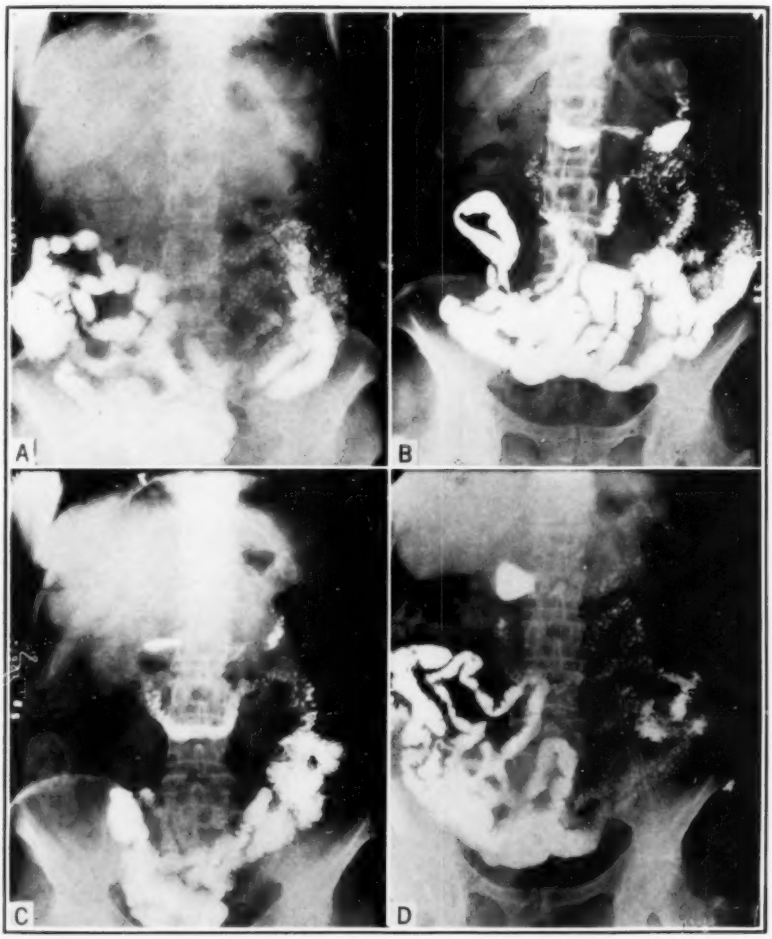

FIG. 2.—Roentgen examination of the gastro-intestinal tract 3 hours after administration of the barium meal: *A*, after 50 days on the deficient diet alone; *B*, 18 days of treatment with thiamin; *C*, 13 days of treatment with thiamin plus riboflavin; *D*, 16 days of treatment with brewer's yeast.

TABLE 2.—ROENTGEN APPEARANCE OF THE GASTRO-INTESTINAL TRACT.

	15 minutes.	1 hour.	2 hours.	3 hours.	4 hours.	5 hours.
Deficient diet	Normal gastric tone;occasional peristaltic rush in proximal jejunum	Motility gradual; pattern herring-bone in jejunum	Stomach empty; same as 1 hr. but barium now in ileum	Barium in ileum; snow flake pattern; ileum normal pattern, slightly widened caliber	Ileum nearly empty; head of meal at sigmoid	
Deficient diet + thiamin	Normal gastric tone; occasional peristaltic rush in proximal jejunum; fine reticular pattern in jejunum	Slow forward progression of barium in jejunum; herring-bone pattern	Delayed ileal motility	Gastric residue; delayed ileal motility	Gastric residue; delayed motility in small intestine; pattern normal	
Deficient diet + thiamin + riboflavin	Normal gastric tone; rapid motility in proximal ileum	Caliber normal; pattern herring-bone with gas in distal loops of jejunum	Barium reached the ileum; normal pattern and tone	Gastric residue; delayed motility in ileum; normal pattern		Stomach empty; barium in cecum; pattern normal
Deficient diet + yeast	Normal gastric tone; rapid motility in proximal ileum	Small intestinal pattern normal	Normal ileal motility	Gastric residue; normal ileal motility; head of meal at cecum		Stomach and jejunum empty; head of meal at hepatic flexure

TABLE 3.—CHANGES IN NEUROLOGIC SIGNS AND ELECTRICAL IRRITABILITY OF THE PERIPHERAL NERVES.

Date.	Therapy. (time in days).	Neurologic signs.							Electrical irritability, μC* (normal 6–9).
		Sensitivity to		Tenderness.		Ataxia.	Corneal reflex.	Smell olfacties (normal 25).	
		Touch.	Pain.	Nerve.	Muscle.				
2/28	Deficient diet (3)	Bilateral hypesthesia, peroneal nerve from ankle to knee: 10–15 mg./mm.^{2} (Normal 6)	Bilateral hypalgesia cut. femoral lat. nerve: 10 g. (Normal 2)	+	0	0	Normal	..	13.7
3/22	Deficient diet (25)	Hypesthesia right cheek	Hypalgesia right cheek	++	+	0	Hyperactive	25	10.0
4/7	Deficient diet (41)	Hypesthesia right cheek	Hypalgesia right cheek	++	+	++ arms	Hyperactive	20	13.4
4/25	Deficient diet (59)	Hypesthesia right cheek	Hypalgesia right cheek	++	+	+++ arms adiadokokinesis	Hyperactive	2	12.4
5/4	Thiamin† (4)	Normal	Normal	0	0	0	Normal	20	15.4
5/17	Thiamin (17)	Normal	Normal	0	0	0	Normal	..	9.6
5/29	Thiamin (29) Riboflavin (10)	Normal	Normal	0	0	0	Normal	..	8.8

* μC = Microcoulombs.

† In the first 3 days the subject received 330 mg. of thiamin. Thereafter she received 60 mg. daily until 5/18, when the dose was reduced to 20 mg. daily for the remainder of the experiment.

clinical signs of peripheral nerve involvement occurred as deficiency progressed. Four days following the administration of thiamin all neurologic symptoms and signs had disappeared except electrical under-excitability. This continued for 17 days after the administration of thiamin, when the response again became normal.

4. Mental Symptoms. Mental symptoms formed a striking part of the clinical picture. During the fifth week of deficiency the subject first complained of nervousness and irritability, which gradually increased in severity. Normally a very optimistic person, she became mentally depressed and frequently wept without cause. She lost all interest in her surroundings and disliked social contact. Sudden noises frequently caused distress although there was no alteration in auditory acuity.* Loss of memory and inability to concentrate were prominent complaints. These symptoms regressed while thiamin was given but were not entirely relieved until yeast was added to the diet. In view of recent knowledge of the rôle of thiamin in the metabolism of brain cells,[10] it is conceivable that these mental changes were more than a simple reaction to a general physical inadequacy but represented true change in cerebral function.

Table 4.—Blood Values.

Period of observation.	R.B.C., millions.	Hgb., gm. per 100 cc.	Hematocrit, vol. %.	M.C.V.,* μ^3.	M.C.Hgb.,† gm. x 10^{-12}.
On admission	4.24	13.45	37.8	89	31.7
Deficient diet (9th week)	3.85 (−9.0%)	13.3 (−0.8%)	37.8 (0.0%)	98.3 (+10.0%)	34.8 (+8.3%)
Deficient diet + thiamin (3d week)	3.40 (−20.0%)	11.9 (−11.0%)	34.7 (−8.0%)	102 (+15.0%)	35.0 (+7.4%)
Deficient diet + thiamin + riboflavin (3d week)	3.42 (−20.0%)	12.9 (−3.7%)	37.0 (−2.0%)	109 (+22.0%)	37.8 (+18.7%)
Deficient diet + yeast (2d week)	3.25 (−24.0%)	12.9 (−3.7%)	38.0 (+0.5%)	120 (+35.0%)	39.7 (+24.0%)
General diet + yeast (4th week)	4.28 (+0.9%)	13.3 (−0.8%)	39.5 (+5.0%)	92 (+3.0%)	31.2 (−2.5%)

* M.C.V. = Mean corpuscular volume.
† M.C.Hgb. = Mean corpuscular hemoglobin.

5. Studies of the Blood. Decrease in the number of red blood cells, increase in mean cell volume and hemoglobin, macrocytosis, polychromasia and poikilocytosis occurred (Table 4). These abnormalities were slight after 9 weeks on the deficient diet alone, but increased in spite of the administration of thiamin and riboflavin. Yeast added to the diet had no apparent effect for the final 2 weeks of the study, but it was continued on discharge from the hospital and 4 weeks later the blood had returned to normal. Dur-

* We are indebted to Dr. O. V. Batson for audiographic studies.

ing this time the subject received a general diet, so that some other factor may have been responsible for the hematopoietic response. However, the fact that a similar type of anemia observed in pregnant women taking a vitamin B deficient diet[35] responded to the administration of yeast suggests the presence in this substance of some active anti-anemic factor other than thiamin or riboflavin.

6. Miscellaneous Observations. Certain general manifestations were evident early in the deficient period. Excessive fatigability was noticed and ultimately became extreme. The skin became pale, flabby and inelastic. The face assumed an expression of despair and the posture suggested extreme fatigue. Edema of the upper and lower extremities, present by the end of the first week, slowly increased. No explanation was found for the edema as the serum protein was normal and cardiovascular abnormalities were insufficient to account for it. Gradual loss of weight occurred in spite of the presence of edema.[4]

When thiamin was administered an immediate improvement was noticeable in strength, general appearance and skin texture. Skin color returned in spite of the fact that the anemia was increasing. Edema subsided and body weight increased. However, this improvement was temporary. After thiamin had been given for 10 days easy fatigability was again present and as described in the previous paper[4] increase in edema occurred and body weight declined. Riboflavin had no significant effect upon these findings, but when yeast was added to the diet the subject returned to normal.

7. Manifestations of Deficiency in 1933 as Compared With 1938. Essentially identical experiments carried out in 1933 and 1938 provide a basis for comparison of the manifestations of induced deficiency. Certain similarities and differences seem worthy of mention. The outstanding clinical manifestations in each instance were changes in body weight, fluid balance and signs referable to the cardiovascular, gastro-intestinal, neurologic and hematopoietic systems. The time of onset of deficiency was comparable, approximately 5 weeks elapsing before signs of deficiency were definite. Anorexia was the first symptom to appear, and in both experiments symptoms preceded physical signs by from 2 to 3 weeks. The development of edema was the only exception.

In 1933, however, glossitis and neurologic abnormalities were prominent, while in 1938 though present, they were comparatively mild. Anemia was more pronounced in the present experiment as were mental and cardiovascular symptoms. While reasons for these differences were not clear, it is of considerable importance to realize that no single sign or symptom can be relied upon to provide a diagnosis of deficiency. A final observation deserves emphasis. Almost without exception the response to individual components of the B complex was both temporary and incomplete and a return to normal occurred only upon the administration of yeast.

Summary. 1. The clinical manifestations of vitamin B deficiency were studied in an otherwise healthy individual who consumed a constant daily amount of a standard diet adequate except for the B complex. These manifestations responded in part to thiamin, were influenced very little by the addition of riboflavin and were relieved by the administration of brewer's yeast.

2. Increase in pulse rate appeared during deficiency. It was associated with symptoms referable to the cardiovascular system. No change in the resting blood pressure, orthodiagram or electrocardiogram was observed. Cardiovascular abnormalities subsided during the administration of thiamin.

3. Gastro-intestinal symptoms developed during deficiency, and were associated with Roentgen evidence of delayed motility in the small intestine. Except for anorexia, which was promptly, though temporarily relieved by thiamin, gastro-intestinal symptoms were not relieved nor was there any improvement in the Roentgen evidence of delayed motility until after yeast was added to the diet.

4. Neurologic symptoms and physical signs were mild and were accompanied by decrease in electrical irritability. These abnormalities disappeared following the administration of thiamin.

5. Mental symptoms were prominent, responding somewhat to thiamin, but were not relieved entirely until yeast was added to the diet.

6. A mild macrocytic anemia developed during deficiency, which was uninfluenced by thiamin or riboflavin but was relieved after the subject had received a general diet and brewer's yeast for 4 weeks.

7. Edema of the upper and lower extremities appeared early in deficiency, was uninfluenced by the administration of thiamin or riboflavin. Gradual loss of body weight occurred in spite of the presence of edema. Edema disappeared and body weight returned to normal only after the administration of yeast.

8. The symptoms and physical signs in the present study were comparable with those observed in the same subject in 1933, although certain differences are described.

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THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS WITH VITAMIN E (TOCOPHEROLS).*

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In a recent paper[5] I reported recovery in 2 cases of amyotrophic lateral sclerosis treated with synthetic vitamin E and discussed the theoretical reasons as well as the experimental knowledge (including references to literature) which led to the initiation of the treatment. Since then I had occasion to treat more than 30 cases. Of these, 15 were carefully observed and consistently treated by me. Five others were treated at the Montefiore Hospital† under my instruction but not under my personal care. These are nonetheless included in this report. The rest of the cases were not adequately studied. Some were seen but once, others were not consistently or sufficiently followed or studied, in still others the question of diagnosis was obviously in doubt.

The results of treatment‡ have confirmed the tentative opinion expressed in the preliminary report. A number of facts have come to light, which require further experimental investigation. Experimental deprivation of vitamin E is now being carried out in monkeys. Creatine-creatinine determinations, liver function studies, investigation of gastro-intestinal enzymes and other vitamin deficiency studies have been carried out in many of the patients. These too will be reported upon as soon as enough facts are gathered. Herein a number of general observations will be discussed briefly to outline the scope of the investigations; thumb-nail case reports to establish the diagnosis in each instance will be given, and a few general conclusions justified by the facts thus far will be drawn. The importance of these studies to other so-called degenerative disease of the nervous system and to their possible relation to problems in internal medicine (cirrhosis of the liver, nephrosis) will also be alluded to. Finally, the clinical observations, particularly as to age, sex and duration of the disease, point to the need for a newer evaluation of the whole clinical syndrome.

Case Reports. Case 1.§—A. L., male, age 52, began to complain of weakness and tiredness of the left hand in July, 1939. He gradually lost

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‡ The Hoffmann-LaRoche Company kindly furnished me the tocopherol acetate tablets for the treatment of all patients under my care and Merck & Co. supplied me with the tocopherol in oil for intramuscular injection. I wish to make herewith grateful recognition and to thank Drs. R. D. Shaner and D. F. Robertson respectively for their most generous help and coöperation.

§ Cases 1 and 2 were previously reported.

power in the hand. Early in October his legs began to tire. When first seen on October 18, 1939, he showed increased deep reflexes on the left side, diminished left abdominals and absent left plantar reflex, weakness of the hand with wrist drop, atrophy of the small muscles of the hand, weakness of the forearm, shoulder girdle, and occasional fibrillations. He was admitted to the Mount Sinai Hospital and treatment was begun on November 13, 1939. Return of power began to appear in a few days, and within a few weeks the wrist drop cleared up and he could use his fingers in skilled movements. On 2 occasions treatment was interrupted for several days and weakness began to return. He has been kept on Ephynal to date and is doing well.

Case 2.—C. B., female, age 36, was admitted to the hospital in August, 1939. Weakness of the arms and legs began in August, 1938. After several months she began to develop difficulty in speaking and swallowing. On examination she showed marked atrophy of the muscles of all the extremities, and particularly of the hand muscles and the tongue; universal fibrillations most marked in the tongue; all the deep reflexes were hyperactive and there was bilateral clonus. The patient was practically bedridden and unable to feed herself. Treatment was begun in October, 1939. The fibrillations disappeared, the tongue began to fill out and to lose its fibrillations and within 2 months she was able to walk. On readmission for purposes of check-up in March, 1940, the patient showed no fibrillations, and was able to walk and feed herself. She is now able to do some housework. She swallows and speaks well. Her diet had been deficient in vitamins in that she ate none of the vegetables containing it.

Case 3.—L. O., male, age 24, was admitted to the Mount Sinai Hospital on January 8, 1940. The disease began in October, 1938, with weakness of the hands and feet. The weakness gradually increased so that he had difficulty in walking and in using his hands. On examination the patient showed steppage gait, inability to walk on his heels, hyperactive deep reflexes, absent abdominals, bilateral Babinski signs, marked atrophy of the deltoids, trapezii and small muscles of the hands with moderate atrophy of the muscles of the thighs, calves and feet. Fibrillations were present in the masseters, tongue, neck, shoulder and arm muscles and the thighs and calves. Treatment was kept up in the hospital for 2 months. The patient stated that he felt better and stronger; actually there was no objective evidence of improvement except possibly for diminution of fibrillations. The condition was regarded as arrested but not improved. While in the hospital he developed pharyngitis during which he showed marked weakness.

Case 4.—L. G., male, age 36, began to have weakness of the legs in March, 1939. For 1 year before the onset of the illness he lived on a restricted diet poor in vitamin E because of gall bladder disease. Weakness of the hands soon followed and generalized fibrillations appeared in June, 1939. When first seen on January 27, 1940, he had marked spasticity in both lower extremities, universally increased deep reflexes with bilateral Babinski reflexes and clonus, generalized fibrillations, weakness of the shoulder and arm muscles and almost complete paralysis of the hand muscles, atrophy of the supra- and infraspinati, deltoids, pectorals and all the small muscles of the hands. Treatment was begun in February and has continued to date. The fibrillations have practically disappeared, walking is somewhat improved and some power has returned in both thumbs. The case may be regarded as definitely arrested and somewhat improved.

Case 5.—R. E., female, age 39, began to have weakness of the hands and forearms in July, 1938. Gradually the legs became weak. It is of interest that she ate few vegetables, little fruit, not much bread, and no cereals or bananas. She was seen in the office on February 7, 1940, when she showed a spastic gait, occasional fibrillations in the triceps muscles and in the right

side of the tongue, markedly increased deep reflexes with clonus and questionable Babinski sign, weakness of all muscles of the hands, biceps, triceps and deltoids on both sides and marked atrophy of all the muscles of the hands. She was admitted to the Mount Sinai Hospital on February 26 and remained for a month. She began to improve rapidly and left the hospital able to walk fairly well and much stronger in the hands. Repeated follow-up examinations since discharge from the hospital showed sustained improvement.

Case 6.—A. R., female, age 49, was admitted to the hospital in a moribund condition on March 25, 1940. The history obtained, because the patient could not speak, was unreliable. It seems that the condition began late in 1937 with weakness of the upper extremities. On admission she had cardiac failure. She drooled saliva, was unable to articulate and could not swallow. Within 24 hours the cardiac decompensation was relieved by treatment. It was then observed that she had generalized muscular atrophy and weakness, practically complete paralysis of the extremities, bulbar and pseudobulbar involvement, with aphonia, dysphagia and explosive laughter and crying, generalized hyperreflexia, except for the eft knee jerk, few general fibrillations but marked ones in the tongue. She had to be tube fed and vitamin therapy administered through the tube. Within a few days she began to show improvement. This continued progressively until she could chew and swallow solid foods. The drooling disappeared, there was no more dysphagia, nor explosive laughing or crying. She could now hold up her head and sit up in bed. Altogether this represented a remarkable and spectacular reversal of bulbar signs and symptoms in a person who was practically dying on admission. The bulbar recovery has been maintained to date.

Case 7.—R. T., male, age 58, was admitted to the Mount Sinai Hospital on March 4, 1940, with the complaints of difficulty in swallowing, inability to speak, and excessive salivation. The condition began very rapidly in April, 1939. The syndrome was essentially bulbar in character. There was generalized hyperreflexia with patellar and ankle clonus. There was slight atrophy of the muscles of the left leg. Fibrillations were very marked and generalized, including the face and the tongue. The tongue could only be protruded as far as the teeth; it showed some atrophy. On treatment the salivation diminished greatly, the swallowing became less difficult. The tongue could be protruded just beyond the teeth. After a stay of 7 weeks, the patient was discharged slightly improved. Only the bulbar involvement seemed to be arrested during the stay in the hospital.

Case 8.—N. W., female, age 40, began to complain of weakness of the hands, 18 months before admission to the hospital on March 22, 1940. In March, 1939, she began to have difficulty in speaking, swallowing and breathing. On admission her speech was unintelligible, she could not hold her head up unsupported and dragged her right leg in walking. Fibrillations were generalized but especially pronounced in the arms, neck and tongue. The left knee jerk was hyperactive, all the other deep reflexes were sluggish. There was a suggestive left Babinski sign. There was bilateral facial weakness, marked weakness of the sternocleidomastoids and trapezii, and the tongue, which was atrophic, could not be protruded beyond the lower lip. There was atrophy of the small muscles of both hands. The patient was unable to turn in bed or sit up without assistance. As soon as the treatment was begun she began to show improvement, and by the time of her discharge on April 13, 1940, her speech had become intelligible, she could hold her head without support and was able to feed herself and walk about the ward. For a few days when she had a mild upper respiratory infection there was a temporary relapse, with rapid recovery when the infection cleared up.

TABLE 1.—RESULTS OF TREATMENT.

No.	Case.	Age.	Sex.	Duration, mos.	Therapy, wks.	Atrophy.	Fibrillations.	Pyr. tract signs.	Bulbar signs.	Defect. vit. E diet.	Other.	Results.
1	A. L.	52	M	3	30	+	+	+	0			Recovered
2	C. B.	36	F	15	26	++++	++++	++++	+++	?		Improved Esp. bulbar
3	L. O.	24	M	15	17	++	++	++	+			Arrested
4	L. G.	36	M	11	13	++++	++++	++++	0	1 yr.	Gall bladder diet	Improved
5	R. E.	39	F	20	13	++	++	++	+			Marked improvement
6	A. R.	49	F	30	6	++++	++++	++++	++++		Heart failure	Marked improvement
7	R. T.	58	M	11	6	+	++	++	+++			Arrested Sl. improved
8	N. W.	40	F	18	6	+++	+++	+++	+++			Marked improvement
9	R. A.	16	F	5	6	++	++	+++	0			Marked improvement
10	P. W.	49	M	11	3	++++	++++	++++	++++	?	Carcinoma pancreas	Improved Died—Pn. Cancer
11	E. H.	45	F	6	5	++	+	++	0	3 yrs.	Bacillary dysentery	Recovered
12	S. Y.	46	M	12	13	+++	+++	+++	++		Pleocytosis Enceph.?	Worse
13	E. H.	37	M	13	14	+++	+++	+++	++	3+ yrs.	Diet deficient	Improved Relapse
14	H. H.	56	F	24	6	++	0	++	0		Hepato-biliary dis.	Arrested Sl. improved
15	W. Z.	21	M	3	4	+	+	++	0			Improved
16	L. G.	60	F	24	8	+++	+++	+++	+++			No change Arrested?
17	R. M.	62	F	17	14	+++	++	+++	0			Worse—bulbar
18	A. K.	49	F	20	14	+++	++	+	++			Sl. worse
19	D. S.	54	M	42	14	+++	++	0	+			Improved
20	J. B.	50	M	8	13	+++	+++	++	++++			Died—Pn.

CASE 9.—R. A., female, age 16, was admitted on March 25, 1940, with the history that in October, 1939, she first noticed weakness of the fingers in typing. Two months later she was unable to approximate the thumb to the tips of the other fingers. At the same time fibrillations were noted in the left arm and right thigh. In February, 1940, weakness of the legs set in, so that she had difficulty in walking, kneeling, and climbing stairs. On occasion she would fall. The weakness of the hands became very

marked. On examination there was atrophy of the small mucles of the hands with early claw-like deformity, poor adduction, flexion, and extension of all the fingers, marked motor weakness in the arms and legs, generalized hyperreflexia with ankle clonus and Babinski signs, absent abdominals, and fibrillations in the deltoids, biceps, hand muscles and thighs. Put on vitamin E therapy, she promptly began to show improvement. Soon she could lift a pitcher of milk, she began to walk without fatigue, the fibrillations decreased markedly, and on discharge, May 2, 1940, she was markedly improved. She has continued to do well. This is the first instance that we know about of amyotrophic lateral sclerosis in a person so young.

CASE 10.—P. W., male, age 59, was admitted on April 23, 1940, with the history that in May of the previous year he began to have weakness of the right hand rapidly involving the right leg and the left arm and leg. His gait became stiff and the fingers of the hand contracted. Very soon he found difficulty in swallowing and speaking and felt twitching of the tongue. On admission he was aphonic, could not swallow and salivated profusely. On examination he showed bilateral hyperreflexia with ankle clonus, fibrillations all over the body and limbs and particularly the tongue which he was unable to protrude. He was only able to raise his right arm and leg a few inches from the bed. As soon as vitamin E was given his swallowing began to improve and his respiratory distress lessened. He seemed to be improving when he developed an acute streptococcus pharyngitis. Swallowing became once more difficult, he developed pneumonia (not aspiration) and died 24 days after treatment was begun. On necropsy carcinoma of the pancreas was found.

CASE 11.—E. H., female, age 45, was first seen on April 2, 1940. She had been suffering from bacillary dysentery for 3 years before the onset of the present illness, which was in September or October, 1939. She ate very little and practically none of the articles of food containing vitamin E. There was also a history of migraine dating back many years. The present illness began with weakness of the left toes, falling on walking downstairs and increasing weakness, which now involved the whole foot and leg. Fibrillations of the thighs were first noticed in February, 1940. On examination she showed left foot drop and a total loss of power in all the muscles of the foot. All the deep reflexes were markedly increased with bilateral clonus, more marked in the left foot, and a suggestive Babinski sign. The left foot and leg showed atrophy. Treatment with vitamin E brought about prompt improvement. Within 2 weeks she discarded a brace which she had been wearing. By the end of the month she could walk on toes and heel, and when last seen on May 7 had recovered most of the power in the foot. Once during the course of observation when treatment was interrupted for a few days, the weakness returned only to disappear with resumption of treatment. Subsequent reports tell of reappearance of fibrillations.

CASE 12.—S. Y., male, age 46, was first seen privately on February 1, 1940. His illness began in February, 1939, with weakness of the right hand, then of both legs, and in June of the same year of the left hand. About a year later his voice began to give out and he complained of choking and difficulty in swallowing. On examination he showed marked atrophy of the muscles of both hands, arms, and shoulder girdles, weakness of both legs, and generalized fibrillations, including the tongue. There was marked hyperreflexia, including the jaw jerks, and extreme loss of power in both upper extremities. The picture was classic of amyotrophic lateral sclerosis, except that the question of chronic encephalitis was raised at a hospital where lumbar puncture was performed and 19 cells were found in the spinal fluid. He was placed at first on 15 mg. of Ephynal daily, and 2 weeks later a diet rich in vitamin E was given. At the end of the third week his swallowing had improved somewhat. The whole wheat germ oil and bile salts

were then added. He continued to improve until the end of April when the condition began to grow worse. Swallowing became more difficult and fibrillations of the tongue became more pronounced. Despite continued treatment the patient has continued to lose ground. He refused to enter the hospital nor would he rest at home. He is a poor junk dealer who was compelled to do what little work he could in order to earn a living.

CASE 13.—E. H., male, age 37, began to have twitching of the right arm, forearm and hand in January, 1939. Two months later the left arm was similarly involved. At this time atrophy of the hand appeared. In July of the same year the legs began to get stiff. On examination the patient showed very spastic gait, marked weakness of both lower extremities, almost complete loss of power in the hands, and weakness of the forearm and shoulder muscles. There was complete atrophy of all the small muscles of the hands and marked atrophy of the arms, forearms, pectorals and leg muscles. There was marked hypertonia in the lower extremities. Fibrillations were numerous in the shoulder, chest, and arm muscles, in the abdomen and thighs and slightly in the tongue. All the deep reflexes were markedly increased; there was bilateral ankle clonus and Babinski sign. Treatment was begun at first with alpha-tocopherol acetate, then followed by the other additions. His gait became more steady, he no longer fell in walking, and the fibrillations seemed to lessen. The condition remained stationary for about 2 months, then began to progress so that the patient is now worse. Of interest in this case is the fact that this patient thrived for some time up to his first visit to the office on a diet almost completely devoid of vitamin E.

CASE 14.—H. H., female, age 56, was first seen on March 30, 1940, when she complained of weakness of the hands and legs. The condition began gradually in 1938, possibly in 1937, and has become progressively worse. In March, 1938, both hands were very weak and in October, 1939, the legs became weak. Physical examination showed generalized weakness with bilateral foot drop, more marked on the right side. There were no fibrillations, the deep reflexes were present and equal but not hyperactive. There was weakness of all the muscles of the hands, of the forearm and arm muscles, of the shoulder girdles and of the dorsiflexors of the feet. There was atrophy of the interossei, thenar and hypothenar eminences, of the forearms, of the left supraspinatus and the peronei of both legs. The presence of hypotonia and the absence of a Babinski sign militated somewhat against the diagnosis of amyotropic lateral sclerosis, but the presence of reflexes, though not increased, and the presence of atrophy spoke in favor of the diagnosis. The patient was put on vitamin E treatment but did not improve; in fact, she seemed to grow weaker. She was admitted to the hospital for further study. There it was found that she had one gall stone and she showed impaired liver function. Treatment restored her appetite and she seemed to improve.

CASE 15.—W. Z., male, age 21, began to complain of weakness of the right hand in January, 1940. The father of the patient insisted that he noticed thinning of the right hand several months before that date. All the deep reflexes were hyperactive. A few fibrillations were noted in the anterior part of the right forearm. There was weakness of the extensor, adductor and opponens of the right thumb, and weakness of the extensors of the wrist and of the first phalanges of the right hand. There was atrophy of the first interroseous space, of the thenar and hypothenar eminences, of the dorsum of the hand and slightly of the forearm and biceps, all on the right side. Intensive treatment was begun on April 26, 1940. On re-examination on June 4, he showed considerable return of power in the hand. The patient no longer tires when writing; he just passed several 4-hour written examinations without fatiguing.

CASE 16.—L. G., female, age 60, began to complain in March, 1938, of generalized weakness. Soon difficulty in swallowing appeared and in the past year progressive dysarthria. The outstanding signs were atrophy and fibrillations of the intrinsic muscles of the hand, general hyperreflexia, including the jaw jerk, bilateral paresis of the palate and the muscles of mastication, and atrophy and fibrillations of the tongue. Altogether this was a very advanced case. Treatment was begun on March 15, 1940. No subjective or objective improvement occurred.

CASE 17.—R. M., female, age 62, began to complain September, 1938, of weakness of the hands and 2 months later of weakness of the legs. On neurologic examination she showed spastic gait with hyperreflexia and ankle clonus and atrophies and fibrillations in the hands, forearms, shoulders and thighs; also aphonia. Despite treatment, which was begun on February 5, 1940, progressive bulbar involvement with dysarthria, dysphagia and atrophy and fibrillations of the tongue appeared.

CASE 18.—A. K., female, age 49, began with dysarthria, hoarseness and pain in the throat followed by generalized weakness in April, 1938. The essential neurologic findings were spastic gait on the right, hyperactive jaw jerk, all other deep reflexes only moderately active, atrophy and fibrillations of the tongue, bilateral atrophy of the deltoids, bilateral motor fifth paresis, deviation of the uvula to the right, and dysarthric bulbar speech. Treatment was begun on February 5, 1940. There has been no improvement to date; indeed, there may have been slight progressive involvement.

CASE 19.—D. S., male, age 54, began to complain August, 1936, following spinal anesthesia for herniorrhaphy, of stiffness and pains in the back of the neck and gradual weakness of the muscles of the shoulders. Following this there was bulbar involvement. On neurologic examination he showed marked atrophy and occasional fibrillations in the muscles of the shoulder girdles and upper arms and hemiatrophy and fibrillations on the right side of the tongue. There were no pyramidal tract signs. Treatment was begun on February 7, 1940. He began to show increasing strength in the muscles of the shoulder so that he could raise the arms and touch the top of his head, something he could not do before treatment. The fibrillations of the tongue disappeared and there was possibly some filling out of the muscles of the right upper arm and shoulder.

CASE 20.—J. B., female, age 50, began to show weakness of the upper extremities in June, 1939, rapidly followed by difficulty in swallowing and progressive involvement of speech. Neurologic examination showed spastic gait, atrophy of the intrinsic muscles of the hands, generalized fibrillations, bilateral involvement of the motor fifth nerve, palatal paresis, bilateral atrophy and fibrillations of the tongue, weakness of the sternocleidomastoids and trapezii, and marked dysarthria. Treatment was begun on February 7, 1940. Despite this she progressed rapidly downward and died on May 13, 1940. (Necropsy to be reported.)

Treatment. The treatment thus far consisted of the administration of Ephynal or alpha-tocopherol acetate by mouth, at first 30 and later 50 mg. daily.* In about one-half of the cases 50 mg. of tocopherol in oil were injected daily intramuscularly. All patients received the following articles of food containing vitamin E, the first three being the richest: lettuce, kale, whole wheat bread, coarse cereals, butter, bananas, fresh corn, fresh peas and beans,

* Prolonged experience indicates that this dose is too small in some cases and that 100 to 200 mg. are necessary.

yolks of eggs, and fat beef. Because vitamin E is fat soluble and because it has been shown that the fat-soluble vitamin K is better absorbed if bile salts are added, 2 5-gr. pills of bile salts were given daily. Where the bile causes diarrhea it is well to give Bilron which contains iron. Every patient received daily 2 teaspoonfuls of whole wheat germ oil. In the past month the extracted rather than the pressed oil was used in the belief that the former is less apt to contain unsaturated fatty acids which may cause deterioration of the vitamin E. Whether the one is more effective than the other cannot be determined from the present studies. Based on the assumption that vitamin B_4 or the filtrate factor, can cause atrophy, the whole B complex has also been given. Whether it is necessary or not is still a question.

TABLE 2.—RELATION BETWEEN DURATION OF DISEASE AND THERAPEUTIC RESULTS.

Duration, mos.	Died.	Worse.	Arrested.	Improved.	Markedly improved.	Recovered.	Cases.
3	..	..	..	..	..	1	1
4–6	..	..	..	1	1	1	3
6–8	1	..	..	..	..	..	1
9–11	1	..	..	2	..	..	3
12–17	..	3	1	1	..	..	5
18–24	..	1	2	..	2	..	5
Over 24	..	..	..	1	1	..	2
Cases	2	4	3	5	4	2	20

TABLE 3.—RELATION BETWEEN SEX AND RESULTS OF THERAPY.

	Died.	Worse.	Arrested.	Improved.	Markedly improved.	Recovered.	Cases.
Males less than 6 months	..	..	..	1	..	1	2
Males more than 6 months	2	2	1	3	..	..	8
Females premenopause	..	..	..	1	4	1	6
Females postmenopause	..	2	2	..	..	..	4
Cases	2	4	3	5	4	2	20

There is some evidence to show that lettuce contains a factor lacking in the germ oil, and, conversely, that there is something in wheat germ oil which is not present in the lettuce; so that the administration of either alone will not cure sterility or abortion in animals, whereas the administration of both will. This is the reason why both the synthetic products and the wheat germ oil as well as the foods rich in vitamin E were given. It is a fact that in 2 cases the administration of alpha-tocopherol acetate alone brought about improvement. In order to insure, if possible, more rapid and pronounced improvement it was thought advisable to saturate the patients and give both the synthetic and natural vitamin E. Now that the fact has been established that improvement can be brought about, one group of patients will be given only the synthetic, the other only the natural vitamin E by mouth. Whether or not the intramuscular injection is superior to oral administration

also cannot as yet be stated. Two patients seemed to show improvement only after the injections were started; in the rest this did not hold. Again, for scientific accuracy, it will be necessary to divide cases into groups for purposes of oral and parenteral administration respectively.

In 2 instances it could be clearly shown that stopping the administration of vitamin E brought about a relapse, which promptly was reversed the moment vitamin E was readministered. This may be of crucial significance. Only two such experiments were purposely undertaken. More such trials will have to be made in the future.

The dosage is not yet established. It seemed at first that 50 mg. of tocopherol daily were adequate. From the work of MacKenzie and McCollum[3] it appears that rabbits need from 0.7 to 1 mg. of tocopherol per kilo of body weight to cure muscle dystrophy. Applying the same figures to humans weighing, say, 60 kilos, it would seem that 50 mg. daily are sufficient. Very probably this is a minimum dose, although it is amply supplemented with the vitamin E in the diet.

The question arises whether patients will have to be treated permanently with synthetic or natural vitamin E. From *a priori* evidence and from observation of patients it would seem that they will, unless of course the cause of failure to absorb is discovered and removed. Why, in view of the fact that natural vitamin E is so prevalent, there is failure of absorption and why if there is failure it occurs only in certain persons and not in others is a question which can be raised but not answered at this time.

One thing may be stated with assurance, namely, that those patients who promise recovery show improvement fairly rapidly. This applies to the disease as a whole as well as to the most recently developed sign which is most likely to recede. The fibrillations are apt to disappear first, thus indicating a recession in the activity of the disease process. These observations are in accord with what is already known of the action of other vitamins. In the first place, it is probably true that the absence of vitamins acts in a specific way upon special tissues. Secondly, the administration of vitamins when effective acts specifically in a curative way. If this is true, it may be pointed out parenthetically that the indiscriminate administration of some or all of the vitamins on so-called general principles is not justified. Thirdly, although partial privation of vitamins over a long period of time may give subclinical manifestations, pronounced clinical syndromes are apt to appear rather rapidly. Fourthly, being specific, the administration of vitamins is apt to bring about fairly rapid recovery even in chronic conditions, always provided that dosage is adequate and absorption effective. It would seem logical to expect that the earlier the case and the more reversible the destruction of nerve tissue the more effective the treatment. In general this is true, but it does not always hold.

Besides there is reason to believe the term reversible may have to be redefined; what appears irreversible now may be shown to be reversible in the future. Nonetheless early and intensive treatment, and this presupposes early diagnosis, is imperative if results are to be obtained.

Analysis of Cases. Study of the three tables will reveal that 11 out of the 20 cases showed varying degrees of improvement. Two patients seem to have recovered, 4 showed marked degrees of improvement and 5 moderate degrees. A. R. (Case 6) was practically moribund, had very advanced bulbar signs, and was expected to die within a few days. The administration of vitamin E by means of stomach tube and intramuscular injection restored completely the functions of chewing and swallowing, and within a short period of a few weeks she could sit up in bed, hold up her head and feed herself. From a bedridden state C. B. (Case 2) now goes about her house, feeds herself and is moderately active. R. A. (Case 9), whose left foot was totally paralyzed, has almost completely recovered its use. Three patients may be said to have the disease arrested. Two patients with very advanced disease and bulbar signs died. One of these began to show improvement in his bulbar signs but died of pneumonia. At necropsy cancer of the pancreas was found, a fact which may prove to be of importance. The other patient died of bulbar involvement. Two patients have definitely grown worse and of the 2 others 1 is worse after initial improvement and the other is only very slightly worse.*

The sex factor is of interest. Except for the 1 male who seems to have recovered, whose illness had been of but 3 months' duration, the 6 patients showing marked improvement were all females, and all were of the premenopause age. One of these women improved remarkably, 1 other improved greatly, 2 recovered from advanced bulbar involvement, 1 other showed marked and 1 moderate improvement. Some improvement occurred in 4 males, and in 1 female in the premenopause age. Two females of the postmenopause age showed what appears to be arrest of the process; only 1 male had the disease arrested. Two males whose illness was of long duration and 2 females of the postmenopause age have grown worse; of the 2 that died both were males. While these facts seem to be important, observation of more cases and over a longer period of time than the 8 months since this investigation was begun will be necessary before drawing final conclusions. It should be stated that the incidence of amyotrophic lateral sclerosis in my whole series is greater in males than in females. Another point worth noting is that neither libido nor potency was affected in the males. Whether men with the disease become sterile is another factor. This point will be investigated. It is relevant to mention in this connection

* Since this paper was submitted for publication 1 patient, L. O., has grown worse and another, R. T., with very advanced disease, died.

that experimental evidence derived from work with animals confirms in some measure the clinical observations. Sterility in female animals, tendency to abortion, or marked reduction in the number of the litters, if brought about by the privation of vitamin E, can generally be reversed by the administration of vitamin E. In males, once sterility is brought about, and particularly if the testes are atrophied, the process cannot be reversed.

Clinical Considerations. Amyotrophic lateral sclerosis has always been regarded as such a sharply defined entity that questions of diagnosis rarely came up. Atrophies, fibrillations and increased deep reflexes are taken to be absolutely pathognomonic. The disease syndrome has been regarded invariably as progressive and ultimately fatal from bulbar palsy within 2 or 3 years. It has always been stated that it occurs past middle life. But the clinical study of the 20 cases herein reported and of 10 additional ones (report of which will appear separately) points to the need of revising some well-established concepts. To begin with, there are at least three and possibly four varieties of amyotrophic lateral sclerosis syndromes. One occurs on the basis of inflammation, generally chronic encephalitis, as Wimmer first showed. Here we are obviously not dealing with a vitamin deficiency. Another small group may be the result of vascular disease, possibly luetic; and in older patients, certain bulbar syndromes, cannot be distinguished from the more usual disease. These, too, are presumably not the result of avitaminosis. In none of these may one expect recovery with vitamin E therapy, but some of those patients may live for years and years. Conversely, the absence of recovery may raise the question whether the syndrome under treatment truly belongs to the third and largest group, namely the so-called degenerative type. It is the last alone which appears to be the result of vitamin E privation and in which favorable response to vitamin E therapy may be expected.

As to age grouping, we have one girl of 16. As far as is known it is the youngest case on record. Two cases occurred in men of 21 and 24 respectively, and 4 others in patients below 40. Only 7 were 50 and over. Another point is the early occurrence of bulbar signs in a large proportion of cases. Usually bulbar symptoms are the last to appear. In some instances involvement of the arms, legs and body was so minimal and the increase of deep reflexes so moderate (sometimes they were absent) that the diagnosis was justly in doubt. This applies to some of the last 5 cases included in this report. Another point worth noting was the excessive salivation in some patients with bulbar involvement. Generally this is attributed to paralysis of the tongue and impairment of swallowing, but in some cases it was so excessive as to raise the question whether the salivatory nucleus in the medulla was also affected. Finally, it is not sufficiently stressed that pseudobulbar symptoms may dominate the bulbar signs and that the loss of voice

and speech may be the result of involvement of the pyramidal fibers as they go from the cortex to the bulbar nuclei rather than of the motor nuclei themselves. That this is true may be inferred in part from the results of treatment. In several patients who responded to the vitamin E the bulbar signs, the more recent ones, cleared up and the patients chewed and swallowed well, no longer salivated and could hold up their heads; whereas the pseudobulbar symptoms, probably the older, responded less well or not at all. This was especially true of Cases 6, 7 and 8. Another point worth recording is the invariable interruption of recovery, sometimes to the point of relapse, by an acute infection, even a mild respiratory one, followed by renewed improvement after the infection was over. This is an observation which seems to hold true in other non-infectious diseases of the nervous system.

Other Degenerative Diseases. If the facts herein presented are correct, two deductions, each of major importance, may be made. First, that vitamin E deficiency, probably of the alpha-tocopherol factor, is one cause of amyotrophic lateral sclerosis and that the administration of vitamin E may be a specific treatment. The importance of this observation, if corroborated by further studies, lies in this, that a so-called degenerative disease hitherto accepted as invariably progressive and fatal, for which there was no treatment and the cause of which was unknown, can be successfully treated in some cases, improved in some others and possibly arrested in still others. Second, these studies open a new page in the understanding and possibly the treatment of other diseases of the nervous system which for want of better knowledge we called degenerative. As a corollary, one may point to the relationship of these studies to the understanding of certain problems in internal medicine. Both hepatic cirrhosis and nephrosis, like degenerative diseases of the nervous system, are end products of obscure pathologic processes which have gone before, and most of the present studies are directed to the elucidation of functions which have been perverted by largely unknown antecedent factors.

Now, the word degeneration is an anatomico-pathologic term usually describing a process which has already spent itself. It tells nothing about causes or pathogenesis. What is meant by the term sclerosis of the nervous system is that myelin sheaths, nerve fibers and nerve cells have disintegrated and glial tissue, that is, a scar, took their place. With other tissues and organs vascular changes and connective tissue scars parallel the glial proliferation. It was dissatisfaction with the label degeneration in the central nervous system, just as it was dissatisfaction with the vague terms toxic and infectious in the case of peripheral nerves, that led to these studies. It has long been suspected that the pathologic processes in so-called degenerative diseases resemble some of the pathologic processes in the nervous system known to be due to vitamin priva-

tion. The recognition that the absence of one vitamin may be the specific cause of one "degenerative" disease, naturally leads to the assumption that other vitamins may play a rôle in the causation of other "degenerative" diseases of the nervous system. This appears to be true, and the evidence at hand justifies a certain amount of theoretical speculation.

A few observations, by way of caution are, however, worth making. First, it does not follow that, because certain syndromes bear some resemblance to each other, they are necessarily related or caused by the same factor. Sclerosis like degeneration, is a final descriptive term. Second, similar clinical end results or disease entities may be the result of different causes. Thus multiple sclerosis is not a disease but a congery of syndromes of varying etiology though the syndromes look clinically very much alike. There are at least three different kinds of multiple sclerosis—possibly more—due to inflammation, allergy and possibly vitamin deficiency. Third, it is well to bear in mind that the nervous system has specific selectivity for drugs, toxins and infections, and different structures react specifically to vitamin, oxygen, sugar or other deficiencies. Certain parts are more sensitive than others and varying structures differ biochemically in their constitution and therefore in their reaction. Add to this the fact already alluded to, that vitamins act specifically, and it becomes clear why analogies alone are not sufficient and why all the degenerative diseases cannot be indiscriminately treated by one vitamin because this vitamin happens to be effective in one of them. From what is known already it may be predicted that certain "degenerative" disease will be found to be the result of the privation of specific vitamins though other factors may play additional rôles. Recent observations that absence of B_6 may be a factor in "degenerative" paralysis agitans, not in the arteriosclerotic or inflammatory types, illustrate the point.

The dystrophies illustrate another syndrome which seems to be the result of vitamin privation. It will be recalled that Bicknell's[2] paper dealt largely with the dystrophies and only incidentally with amyotrophic lateral sclerosis. He reported recoveries in several patients treated with wheat germ powder. He did not use the synthetic vitamin E or the tocopherols. More recently Stone,[4] reported on the treatment of muscular dystrophies and "allied" conditions with vitamin E. As has been pointed out, "allied" is a vague term and should not be used. But Antopol and Schotland[1] reported good results after treatment of dystrophies with vitamin B_6. It is also worth noting that the dystrophies belong to the so-called heredo-generative diseases. That is, there seems to be a genetic factor in addition to vitamin deficiency. My own experience is limited to a few patients with dystrophies, all of whom have been treated both with the synthetic as well as the natural vitamin E. In none have I seen thus far rapid or really pronounced

recoveries. The patients say they feel better. One believes that he is stronger and one rises normally from a supine position instead of climbing upon himself as he did previously. Much further study is necessary to justify positive conclusions, though the evidence so far adduced is worthy of the utmost consideration.

Conclusions. 1. Twenty cases of amyotrophic lateral sclerosis treated with vitamin E have been studied and the results reported.

2. Privation of vitamin E plays a specific rôle in the causation of some types of amyotrophic lateral sclerosis, but other factors also operate in an as yet unknown manner.

3. Synthetic vitamin E (*i. e.*, alpha-tocopherol) and natural vitamin E act specifically in some cases and bring about varying degrees of improvement, perhaps in inverse ratio to the age and duration of the disease process. Some cases, for reasons not yet clear, fail to respond despite intensive treatment.

4. Dietary deficiency, gastro-intestinal and hepatic disease, possibly the absence of other vitamins, may play additional causative rôles. Some of the evidence points to interference with the absorption of the vitamin E.

5. There is evidence pointing to the probability of vitamin deficiency in the causation of other degenerative diseases and to the need of specific vitamin treatment if treatment is to be effective and scientific.

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SULFATHIAZOLE IN THE TREATMENT OF PNEUMOCOCCUS PNEUMONIA.

COMPARATIVE STUDY UTILIZING SULFAPYRIDINE THERAPY.

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THE preparation of therapeutically effective synthetic derivatives of sulfanilamide has been demonstrated by the conjugation of sulfapyridine. The possibility of further compounds is illustrated

by the report of Fosbinder and Walter[4] who describe several new sulfanilamide derivatives, among which is sulfathiazole. This preparation was independently synthesized by Lott and Bergeim.[7] Sulfathiazole (2-para-amino benzene sulfonamide thiazole) is apparently readily absorbed from the gastro-intestinal tract, thus resembling sulfanilamide rather than sulfapyridine. The studies of the blood level concentration and the urinary secretion also simulate the action of sulfanilamide, in that high blood levels are quickly attained and excretion in the urine occurs at a rapid rate. The degree of conjugation in both the blood and urine is much less than that which occurs with sulfapyridine. As a consequence, a larger percentage of the total drug absorbed into the blood stream is therapeutically active. Chemotherapeutically considered, acetylated sulfanilamide compounds are inert.

The preliminary studies have indicated that sulfathiazole equals sulfapyridine in therapeutic effectiveness when comparative studies were made with various types of experimental pneumococcus infections. On the other hand, staphylococcus infections respond more readily to sulfathiazole medication. However, because of the paucity of available published reports, the evaluation of the effectiveness and toxicity of sulfathiazole must await further clinical and experimental data. This clinical study presents a contribution to such data.

Method of Study. The dosage of sulfathiazole consisted of 4 gm. (8 tablets) initially followed by 1 gm. every 4 hours, day and night, until the temperature remained normal for 48 hours when medication was discontinued. Thirty-five patients received 4 gm. initially followed by dosages of 3 gm., 2 gm. and then 1 gm. at the subsequent 4-hour intervals respectively. The blood levels were not appreciably affected by this procedure. Serum was not combined with sulfathiazole nor is the use of intravenous sodium sulfathiazole here reported. Proved typed pneumococcus pneumonias with physical signs and positive Roentgen ray evidence are reported in this study. Thorough routine investigation included blood counts, blood cultures, urinalysis, with the blood sulfathiazole determinations computed after 24 hours of drug regimen. Adjunct therapeutic measures were utilized such as oxygen, intravenous fluids, and other drugs. It must be stated that these accessory methods were infrequently employed. For example, oxygen was used in only 5 cases. The attempt was thus made to evaluate the drug alone under severe clinical conditions. The clinical material was unselected in a large charity hospital. A contemporary comparative study included a series of patients treated with sulfapyridine alone, or combined with immune serotherapy. The age, sex, types of pneumococci, bacteremic incidence and contemporary time occurrence in this sulfapyridine series furnish practically an alternate case control study for sulfathiazole.

Results. This report comprises 169 patients treated by peroral sulfathiazole. Table 1 illustrates the results obtained in the individual types of pneumococcus infections. The deaths in the total series of 169 patients were 9 in number (5.3%). Of the nonbacteremic group in this series 7 died (4.8%). Twenty-four posi-

tive blood cultures were encountered, an incidence of 14.2% in the entire series; there were 2 deaths in this group (8.3%). The bacteremic investigation was interrupted for 18 patients because of the lack of supply of available culture medium for several days. Several positive cultures would undoubtedly have resulted. Nevertheless,

TABLE 1.—SULFATHIAZOLE-TREATED PATIENTS.

Type.	Total.			Non-bacteremic.			Bacteremic.		
	No. of cases.	Deaths.		No. of cases.	Deaths.		No. of cases.	Deaths.	
		No.	%.		No.	%.		No.	%.
I	27	3	11.1	19	2	10.5	8	1	12.2
II	75	3	4.0	62	3	4.8	13	0	0
III	19	3	15.8	18	2	11.1	1	1	100
IV	8	0	0	8	0	0	0	0	0
V	6	0	0	6	0	0	0	0	0
VII	15	0	0	14	0	0	1	0	0
VIII	13	0	0	13	0	0	0	0	0
XIV	1	0	0	0	0	0	1	0	0
XIX	1	0	0	1	0	0	0	0	0
XXI	1	0	0	1	0	0	0	0	0
XXV	2	0	0	2	0	0	0	0	0
XXVII	1	0	0	1	0	0	0	0	0
Total	169	9	5.3	145	7	4.8	24	2	8.3

Incidence of bacteremia, 14.2%.

TABLE 2.—SULFAPYRIDINE AND SULFAPYRIDINE COMBINED WITH SERUM.

Type.	Total.			Non-bacteremic.			Bacteremic.		
	No. of cases.	Deaths.		No. of cases.	Deaths.		No. of cases.	Deaths.	
		No.	%.		No.	%.		No.	%.
I	37	0	0	33	0	0	4	0	0
II	61	4	6.5	49	2	4.1	12	2	16.6
III	14	0	0	13	0	0	1	0	0
IV	10	0	0	9	0	0	1	0	0
V	4	0	0	4	0	0	0	0	0
VII	14	2	14.2	11	1	9.1	3	1	33.3
VIII	9	0	0	8	0	0	1	0	0
IX	1	0	0	1	0	0	0	0	0
X	1	1	100	1	1	100	0	0	0
XV	1	0	0	1	0	0	0	0	0
XVII	1	0	0	1	0	0	0	0	0
XVIII	1	0	0	0	0	0	1	0	0
XIX	1	0	0	0	0	0	1	0	0
XX	2	0	0	2	0	0	0	0	0
XXIII	5	0	0	5	0	0	0	0	0
XXV	1	0	0	1	0	0	0	0	0
XXVII	1	0	0	1	0	0	0	0	0
Total	164	7	4.2	139	4	2.8	25	3	12

Incidence of bacteremia, 15.2%.

these 18 are included in the non-bacteremic group. There were 63 patients (38%) over 40 years of age. Eight of the 9 deaths occurred in patients beyond 40 years. The contemporary sulfapyridine-treated series which included 69 serum combinations totaled 164 patients with 7 deaths, a percentage of 4.2; there were 4 deaths (2.8%) in 139 non-bacteremic cases, while of 25 patients with posi-

tive blood cultures 3 died (12%). The bacteremic incidence was 15%. Table 2 summarizes the results for the various types of pneumococci. There were 71 patients (43%) over 40 years of age in the sulfapyridine series. Three of the total of the 7 deaths were encountered in this age group.

Blood Concentration of Sulfathiazole. Sulfathiazole appears rapidly in the blood stream following oral administration. The blood levels are relatively high when compared to sulfapyridine, averages well over 6 mg. per 100 cc. being readily attained. These levels are not as constantly maintained, greater variations occurring on the maintenance dose than with sulfapyridine. For example, in the daily blood determinations on B. W. from April 23 to 29, 1940 inclusive, the readings were 9, 7, 5, 5, 3, 5, 2, 8 and 4 mg. per 100 cc. respectively. The initial determination (9 mg. per 100 cc.) was made 19 hours after the onset of medication. Thirty-six hours after the drug was discontinued no traces of the drug were found in the blood or urine. The drug is eliminated rapidly from the blood stream, clearing frequently within 24 hours after drug cessation. The drug similarly disappears from the urine in 24 to 36 hours. The conjugated form constitutes a very small fraction of the total blood content. An analysis of 100 determinations showed an average of only 4% conjugation in the total blood sulfathiazole. The acetylated fraction of the total sulfathiazole content in the urine similarly is very much less than occurs with sulfapyridine. The analysis revealed an average of 13% conjugation in the urine. While it is difficult to correlate clinical response to a definite blood concentration of the drug, 6 mg. per 100 cc. seems an apparently satisfactory level in the light of our experience.

Untoward Effects of Sulfathiazole. Seven patients experienced nausea and vomiting, 1 requiring cessation of the drug. No evidence of renal irritation, gross or microscopic hematuria, anuria or nitrogen retention could be attributed to the drug in this clinical experiment. Similarly, no marked effect was induced on the hemopoietic system. Hemolytic anemia was not encountered. Liver damage clinically was not found. Drug fever and drug rashes appeared. Five patients, 2 of whom succumbed, developed a drug rash diffusely distributed on the face and extremities; 3 were in the form of dark red nodules, 0.5 to 1 cm. in diameter, distinctly elevated and very firm. All 5 patients were very ill and had high temperatures. Two developed an erythema multiforme type of eruption. Two had, in addition to the rash, an intense conjunctivitis. The 3 patients who survived had received 20, 30, and 16 gm. respectively of the drug, while the 2 fatal cases had taken 30 and 75 gm. respectively. The blood levels ranged from 5 to 10 mg. per 100 cc. One additional instance of marked conjunctivitis was noted. While the toxic reactions encountered are similar to those experienced with sulfanilamide and sulfapyridine, the comparative

toxicity approaches sulfanilamide in that the reactions are distinctly less frequent and milder.

Complications. Empyema has been a relatively frequent complication this season, encountered on all therapeutic regimens. Seven patients developed empyema in the sulfathiazole-treated group,

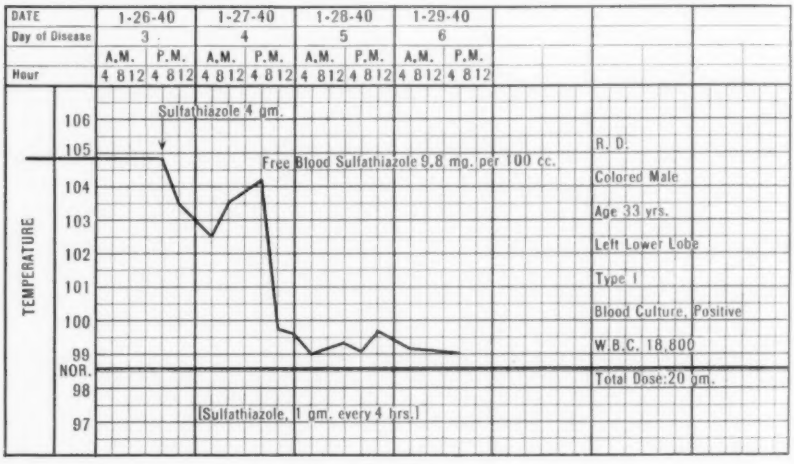

CHART I.

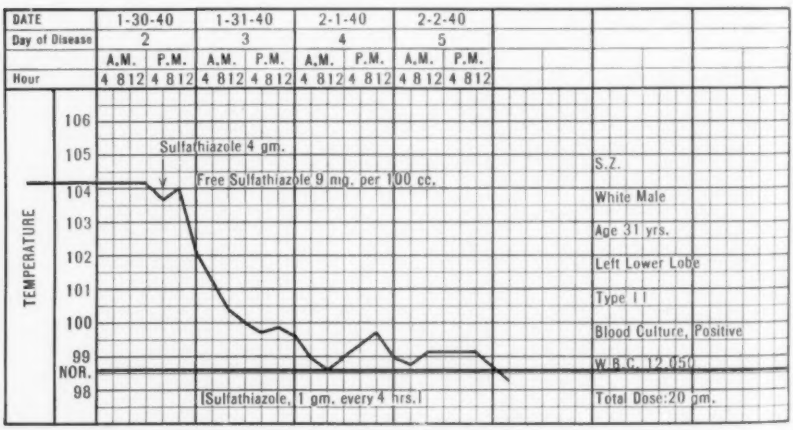

CHART II.

while 4 occurred in the sulfapyridine series. Three sterile effusions developed. One patient showed a pericarditis. Two instances of delayed resolution were noted. The sulfathiazole group is remarkably free from pyogenic complications such as otitis media, mastoiditis, endocarditis and meningitis.

Comments. The satisfactory clinical response to sulfathiazole in pneumococcus pneumonia is revealed by the course of the temperature curve. This shows a characteristic combination of crisis and lysis without the precipitous termination of the former and the absence of the prolonged course of the latter. This may be described as a concave trajectory curve, or geometric hyperbola with the normal temperature level attained in the 48- to 60-hour period.

Charts 1 and 2 are characteristic of the termination described and contain the essential pertinent data, illustrating the effect in a Type I and Type II bacteremic infection respectively. Table 3 compares the hour period in which the temperature reached and remained at the normal level, following the onset of medication.

TABLE 3.—NORMAL TEMPERATURE FOLLOWING ONSET OF MEDICATION.

	Sulfathiazole.		Sulfapyridine.		Sulfapyridine combined with serum.	
Hours.	No.	%.	No.	%.	No.	%.
24	60	37.4	39	40.6	21	34.4
48	59	36.9	41	42.7	28	45.9
72	16	10.0	6	6.2	2	3.2
More than 72	25	15.6	10	9.6	10	16.2
Totals	160		96		61	

The comparison includes sulfathiazole, sulfapyridine, and sulfapyridine combined with immune serotherapy. Temperature reduction is produced more rapidly by the sulfapyridine therapy, although the differences are not pronounced. Comment must be made of the clinical impression created by the patient with pneumonia treated with sulfathiazole. When comparison with sulfapyridine therapy is made, the relative comfort of the patient on sulfathiazole, the absence of vomiting and the greatly diminished indication for parenteral fluids stand out prominently.

Summary and Conclusions. The following quotation from Long[6] is both timely and necessary: "The evaluation of these new chemotherapeutic compounds will necessitate extensive experimental and clinical investigations in order to determine their efficiency in the control of infections and their clinical toxic manifestations. Until the time when such data are in hand, it is hoped that enthusiasm does not outrun common sense."

1. One hundred and sixty-nine patients with typed pneumococcus pneumonia were treated with peroral sulfathiazole with 9 deaths, a 5.3% mortality.

2. A control series in which sulfapyridine combined with serum was utilized shows slightly better results, namely a 4.2% mortality, although the mortality in the bacteremic group was higher with sulfapyridine treatment.

3. Sulfathiazole is apparently equally as effective a therapeutic agent as sulfapyridine in the treatment of pneumococcus pneumonia.

4. Sulfapyridine showed more effectiveness in the therapy of Type I and Type III infections, whereas sulfathiazole produced better results in infections by Types II and VII.

5. Nausea and vomiting and the other common toxic manifestations of sulfapyridine therapy are much less frequent with sulfathiazole.

6. Drug fever and especially the papulonodular eruption with conjunctivitis are severe toxic manifestations of sulfathiazole medication.

7. The blood concentration level varies considerably in the same individual on the ordinary maintenance dose of 1 gm. every 4 hours.

The Squibb Institute for Medical Research, New Brunswick, N. J., kindly provided the sulfathiazole for use in this investigation.

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SULFATHIAZOLE TREATMENT IN RESPIRATORY INFECTIONS.

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During the winter of 1939–1940, 52 cases of respiratory infection seen at the University and Graduate Hospitals of the University of Pennsylvania were treated with sulfathiazole. In each of these cases there was an initial diagnosis of pneumonia. In all cases specimens of sputum were examined for pneumococci and in the great majority chest Roentgen rays were obtained and blood cultures were taken before treatment was started. There were 34 white patients and 18 colored, 25 male patients and 27 female. The majority fell in the age group of 15 to 40 although there were 11 over 50 years.

Thirty-seven turned out to be typical cases of pneumococcal pneumonia. In 6 of these there were positive blood cultures. The

type of pneumococci encountered are shown in Table 1. It will be noted that 13, or one-third of the group, fall in the first three types. This fact plus the high incidence of blood stream infection is good evidence of the severity of the type of infection.

TABLE 1.—TYPES OF PNEUMOCOCCI.

	Cases.		Cases.
1	8	8	5
2	1	14	1
3	4	17	1
4	3	18	2
5	5	19	1
6	1	33	3
7	3		

There were 11 cases of atypical or bronchial pneumonia. In 3 cases pneumococci were found in the sputum. In 2 others *Strep. viridans* was found and in 1 a non-hemolytic streptococcus. In the remainder no predominant organisms were found. There were no cases with positive blood cultures in this group.

In 4 cases the final diagnosis was bronchitis because of negative chest Roentgen rays and the paucity of chest signs on physical examination. In 3 cases the predominant organism in the sputum was a pneumococcus and in the fourth a *Strep. viridans* was found. The types of pneumococci found were 4, 8 and 33.

Dosage. An initial dose of 3 gm. of sulfathiazole (by mouth) was given, followed by a second dose of 3 gm. in 4 hours. Then 1 gm. was given every 4 hours until treatment was discontinued. In general, therapy was continued for 2 or 3 days after the temperature had fallen to normal.

Antipneumococcic serum was not withheld if at the end of 24 to 48 hours there had not been clinical improvement. Serum was given in 4 of the typical pneumococcal pneumonias, 3 of whom died and in 2 of the atypical pneumonia patients both of whom were fatalities.

Results. Of the 37 patients with typical pneumococcic pneumonia, 2 died, giving a mortality rate in this small group of 5.4%. These same 2 deaths were also the only fatalities among the 6 cases with blood stream invasion. Of the remaining 4 cases with positive blood cultures that recovered, 2 had both serum and sulfathiazole. One of these last 2 had a severe Type 1 infection and was not improved after 24 hours of sulfathiazole therapy. The other patient had developed a positive blood culture while taking sulfapyridine and was then shifted to sulfathiazole in large dosage without improvement. An empyema occurred while on sulfathiazole but he eventually recovered perhaps in spite of both drugs as the infecting organism, a Type 4 pneumococcus, was found to be highly resistant to both sulfapyridine and sulfathiazole in *in vitro* experiments.

The temperature fell to normal in 24 hours in 16 patients and in 48 hours in 12 others. In 6 cases the temperature did not reach normal for 96 hours. A secondary rise in temperature occurred in

8 cases after the temperature had been normal for 24 hours. In 1 case this secondary rise was caused by drug fever, in another by a complicating thrombophlebitis but in the other 6 no etiologic cause was determined. The 1 case of thrombophlebitis which occurred on the eighth day of treatment and an empyema which cleared up on chemotherapy and thoracentesis constituted the only complications to the pneumococcic infection.

Clinical Abstracts of Fatal Cases. CASE 1.—A. S., 63-year-old white male, admitted to the University Hospital on the sixth day of his illness. On examination his temperature was 102.4° F., pulse 118 and respirations 44. Chest Roentgen ray showed density of the right upper and lower lobes and the left upper lobe. A Type 1 pneumococcus was recovered from the sputum. The white blood count was 9800 with 94% neutrophils.

On the second hospital day the blood culture taken on admission was reported as showing 130 colonies of Type 1 pneumococcus per cc. of blood. Another blood culture was taken at once and later the patient was given 200,000 units of Type 1 antipneumococcic rabbit serum. This second blood culture taken before the serum therapy and after 24 hours of sulfathiazole therapy showed growth only in the flasks; the plates were sterile. On the fifth hospital day the blood culture was negative and although the temperature did not go above 99.4° F., the patient did not appear clinically improved. Serum was again given 2 days later and in spite of continued sulfathiazole therapy the temperature rose to 102° F., the patient became weaker; the lungs filled with fluid and the patient died.

CASE 2.—F. B., a 58-year-old colored man, admitted to the Graduate Hospital on the second day of his disease. He gave a past history of hypertension and asthma. Examination disclosed an elderly appearing colored man in acute distress. The temperature was 101.6° F., pulse 120, and respirations 40. Physical examination and Roentgen ray showed involvement of the right lower lobe and part of the right middle lobe. Laboratory studies revealed a Type 8 pneumococcus in the sputum, 4.3 millions red blood cells, 66% hemoglobin and 8000 white blood cells with 85% neutrophils. The Wassermann reaction was 4+.

After 2 days with but little improvement the sulfathiazole was increased to 12 gm. per day and 200,000 units of Type 8 pneumococcic antisera were given. The blood level of sulfathiazole as run by the inadequate methods available (*vide* next paper) was 2.2 mg. per 100 ml. after the first 24 hours but rose to 17 mg. per 100 ml. on the 12 gm. per day dose and was 10.5 mg. for 100 ml. the day before death.

Twenty-four hours before the patient died (on the ninth hospital day) he appeared fairly well and his temperature, pulse and respiration were down. In 6 hours, however, he relapsed, developed peripheral circulatory collapse and died. The total sulfathiazole dose was 66 gm.

At *autopsy* the important findings were: an acute, severe hemorrhagic gastritis, consolidation of the right upper lobe, the right lower lobe and part of the right middle lobe, cloudy swelling of the liver, luetic aortitis and early nephrosclerosis. There were no crystalline deposits in the kidneys or urinary passages.

In the group of 11 atypical pneumonias 3 patients died. There were no cases with positive blood culture. The temperature fell to normal in 8 of the cases within 24 hours. There were no complications.

CASE 3.—L. K., a 68-year-old white male with diabetes and cancer of the bladder, suddenly developed a temperature of 104° F., pulse 114, respirations 30, while in the University Hospital. Physical examination and Roentgen ray disclosed a consolidation of the left lower lobe of the lung. Examination of the sputum revealed a predominance of *Strep. viridans* and a moderate number of hemolytic *Staph. aureus*. The blood count showed 3.4 million red blood cells, 60% hemoglobin and 14,000 white blood cells with only 55% neutrophils. The blood culture was negative.

After apparently improving, the temperature not going over 99.8° F. on the seventh day of illness, a toxic erythema and edema of the back of the hands occurred on the tenth day and the temperature rose to 104.2° F. On the eleventh day the drug having been discontinued after a total of 50 gm. the temperature remained normal. Three days later, the temperature again rose and the patient died. The blood level was 6.7 mg. per 100 ml. on the second day of treatment and 4.6 mg. per 100 ml. on the ninth day.

CASE 4.—C. K., a 53-year-old white male was being prepared for operation for cancer of the lung at the University Hospital. He suddenly became acutely ill with a temperature of 104° F., pulse 120 and respirations 38. Physical examination disclosed consolidation of the right upper lobe and right middle lobe. A Type 22 pneumococcus was recovered from bronchoscopic drainage. The blood count showed 3.4 millions red blood cells, 69% hemoglobin, 22,100 white blood cells with 92% neutrophils.

Sulfathiazole was started in the usual dosage and 100,000 units of Type 22 pneumococcic antiserum were given daily for 3 days. On the third day the blood culture was reported as positive for Type 18 pneumococcus. Of Type 18 antiserum, 100,000 units were therefore given and repeated for 3 days.

The temperature fell by crisis on the fourth day of the disease and remained practically normal for 2 days. It then rose rapidly and the patient died on the ninth day. The sulfathiazole was stopped on the seventh day after red blood cells and sulfathiazole crystals were found in the urine. The total dose was 35 gm.

At autopsy a bronchogenic carcinoma of the right main bronchus of the lung was found with massive secondary lesions of the liver. There were multiple abscesses of the right lung with bronchopneumonia and pyopneumothorax. The kidneys were not examined.

CASE 5.—M. H.,[4] white female, aged 77, had had a chronic cough for 6 months associated with slight dyspnea on exertion for 3 months prior to admission. Two weeks before admission her cough became worse and she was referred to the University Hospital with a diagnosis of pneumonia. Examination revealed an acutely ill woman with a temperature of 102.6° F., dyspnea and slight cyanosis. There were physical signs of involvement of both lower lobes. Roentgen ray showed density of the entire left chest and the right lower lobe. A Type 3 pneumococcus was recovered from the sputum. The blood culture was negative. The white blood count was 15,600 with 90% neutrophils.

A diagnosis of atypical pneumonia was made and sulfathiazole given in the usual dosage. Intractable nausea and vomiting ensued which lasted until the medication was discontinued at the end of the fourth day. Daily parenteral infusions of saline and glucose were given. On the third day abundant albumin was found in the urine and on the fourth day there was still abundant albumin plus the additional discovery of microscopic hematuria. It was also felt that the urinary output was falling so that the sulfathiazole medication was discontinued after a total of 24 gm. had been given.

On the fifth hospital day all the urine passed was obtained by catheter.

The amount totalled 160 cc. Albumin was abundant and there were many hyaline and granular casts. On the sixth day the total urine output consisted of 225 cc. obtained by catheter. On the eighth day the urinary output had risen to 575 cc. but the patient was clinically worse so that 100,000 units of Type 3 antipneumococcus rabbit serum were given. Two days later after a short period of improvement the patient suddenly died.

Necropsy (salient features only). Both kidneys (160 gm. each) were large and soft. The cortices were narrowed, finely granular and pale reddish-pink in color. The pyramids were large and contained small hemorrhages and prominent streaks of "gritty" crystalline material which converged at the apices and extended into the calices as short fragile cords. Gritty sandlike material was found in the pelves and urinary bladder. On analysis this gritty material was composed of a derivative of sulfathiazole. The lungs showed marked peribronchial and perivascular fibrosis and a mild degree of bronchopneumonia. There was an acute hemorrhagic pancreatitis and a patent foramen ovale.

The group of 4 patients with bronchitis, 3 pneumococcol, is worth mentioning because of the uniformly good results. The temperature fell abruptly to normal in 24 hours in each case and there was marked improvement in the clinical condition coincident with this fall.

Toxicity. The various toxic reactions and their incidence are shown in Table 2. It will be noticed that vomiting occurred in only 8 of the entire group of cases and in only 1 of the 8 was this severe in nature. Microscopic hematuria was present in 4 patients and crystals of sulfathiazole or acetyl sulfathiazole were found in the urine of 12. One patient (M. H.), previously reported[4] in greater detail, was found at autopsy to have concretions of acetyl sulfathiazole within the collecting tubules of the kidneys.

TABLE 2.—TOXIC REACTIONS WITH SULFATHIAZOLE.

	Typical group.	Atypical group.
Vomiting	6 (1 severe)	2
Urine—		
Renal concretions with oliguria (autopsy)	0	1
Crystals	10	2
Microscopic hematuria	2	2
Dermatitis	0	3
Headache	2	0
Psychologic difficulties	1 (depressed)	0
Conjunctivitis	1	0
Fever (drug)	1	0
Icterus	1 (4th day of treatment — urobilinogen 1 to 50)	0

Three patients developed a toxic dermatitis. This took the form of a lesion very closely simulating erythema nodosum. The eruption tended to be bilaterally symmetrical and on the extensor surfaces of the arms and legs. One patient developed toxic conjunctivitis such as described by Haviland and Long.[3] One patient was noticed to be slightly icteric on the fourth day of treatment

and was found to have a positive test for urobilinogen in the urine in a dilution of 1 to 50. There was little or no fall in red count or hemoglobin.

Discussion. Our results in this small series of cases closely approximate those described by others.[1,5,6] Sulfathiazole given in slightly larger doses than sulfapyridine effects cure in pneumonia in about the same percentage of cases as does sulfapyridine. The temperature does not fall quite so abruptly perhaps, with sulfathiazole as with sulfapyridine, but this fact is overshadowed by the great reduction in the incidence of nausea and vomiting with the use of sulfathiazole. It is interesting to note that all of our fatalities were among the 11 patients over 50 years of age. This gives a perfect record for cures in the other 41 patients and a mortality rate of 45% in the cases over 50 years of age. This emphasizes a very important point. The fatalities in adequately treated pneumonia do not occur in the young, healthy individuals but in the debilitated, elderly patient with complicating disease. All 5 of our patients who died improved temporarily under treatment but later relapsed. In 4, there were complicating disease conditions present. Case F. B. had hypertension, asthma and syphilis; L. K. had diabetes and cancer of the bladder; C. K. had cancer of the lung with metastasis to liver; and M. H. had congenital heart disease and marked pulmonary fibrosis.

In both drugs, the greatest danger appears to lie in the re-crystallization of the free, or, more frequently, the acetylated drug within the urinary passages. With sulfapyridine this crystallization occurred most frequently within the renal pelves and ureters. Sulfathiazole, however, perhaps due to the fact that it is not reabsorbed in the collecting tubules crystallizes out both in the experimental animal[2] and man within the renal tubules. Fortunately, sulfathiazole is not acetylated to as large an extent as sulfapyridine for, although pure sulfathiazole is almost twice as soluble as pure sulfapyridine, the acetylated forms of both drugs are very insoluble. There is certain evidence that by giving alkalies (*vide* next paper) with these drugs the danger of urinary concretions is lessened. Certainly in the majority of our cases it seemed possible to control the crystalluria by increasing fluid intake and giving sodium bicarbonate. However, in view of the small differences in solubility of the acetylated sulfathiazole crystals in the range of pH found in urine, it is probable that the reduction in numbers of crystals was due more to the increased fluid intake.

We feel, therefore, that the best means of avoiding the renal complications from either sulfathiazole or sulfapyridine consists in an adequate fluid intake, at least 2500 cc. a day, parenterally if necessary, giving an alkali, sodium bicarbonate or sodium lactate, keeping an accurate intake-output chart, and daily urinalyses particularly during the first few days of treatment.

Summary. Fifty-two cases of respiratory infection were treated with sulfathiazole. There were 37 cases with typical pneumococcic pneumonia with 2 deaths (a mortality of 5.4%), 11 cases of atypical pneumonia with 3 deaths, and 3 cases of pneumococcic bronchitis, all with prompt improvement. The toxic reactions of sulfathiazole are discussed.

We wish to thank E. R. Squibb & Sons for supplying us with the sulfathiazole used in this study.

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SULFATHIAZOLE IN BLOOD AND URINE.

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In view of the recognized value of sulfathiazole as a chemotherapeutic agent, it would seem desirable to ascertain optimal levels of concentration at which this drug might be maintained in the circulation. The methods currently employed for the analysis of sulfathiazole in blood are recognized as inadequate,[5a,8,9] since recovery of the drug when added to whole blood is uniformly low. In this paper we wish to report observations regarding the difficulties encountered in the analyses and to offer a procedure of analysis applicable for clinical purposes. Moreover, since the greatest danger in the use of the drug appears to be the occurrence of crystalline concretions in the urinary passages,[1,3,4,8–10] studies are reported relating to the excretion of the drug in urine, its solubility, and crystal structure.

Recovery of Sulfathiazole Added to Whole Blood, Serum and Normal Urine, Respectively. The addition of sulfathiazole to whole blood to give samples containing 5 to 15 mg. per 100 ml. yielded in 18 duplicate analyses an average of 86.4% recovery. The analyses were made by applying the Marshall and Litchfield method[7] for determination of sulfanilamide to the measurement of sulfathiazole.*

* It should be noted that Bratton and Marshall[6] at the time of their publication advised caution in applying the method for the determination of sulfanilamide to other sulfonamide preparations that might be used therapeutically at a later time.

The diminutions in recovery were obtained whether diazotization and coupling were carried out in an ice bath or at room temperature; whether N-(1-naphthyl)-ethylenediamine or dimethyl-alpha-naphthylamine was used as the coupling component; or whether oxalated, citrated, or defibrinated blood was employed. Treating the protein-free filtrates of the prepared whole blood samples with 0.5 N HCl and heating in a boiling water bath for 1 hour did not alter the percentage of sulfathiazole that was recovered.

In several series of analyses sulfathiazole was added to the blood before precipitation of the proteins and to the filtrates after precipitation of the proteins. A comparison of the results of these determinations indicated that although approximately 14% of the drug was lost when it was added to whole blood, practically complete recovery was obtained when the drug was added to blood filtrates after protein precipitation. Since the loss of sulfathiazole occurred during the precipitation of proteins with trichloracetic acid, other protein precipitants were investigated. A list of the protein precipitants studied is given in Table 1, together with the percentages of recoveries obtained. It will be seen that all of the protein precipitants that were tried yielded unsatisfactory recovery of the drug.

TABLE 1.—RECOVERY OF SULFATHIAZOLE USING VARIOUS PROTEIN PRECIPITANTS.

Precipitant.	Percentage recovery (average of 6 or more analyses).
Trichloracetic acid	86
Heat and trichloracetic acid	89
Tungstic acid	59
Metaphosphoric acid	72
Toluenesulfonic acid	81
Alcohol-acetone	85
$ZnSO_4$-NaOH	Unsatisfactory*
Ethyl alcohol	Unsatisfactory†

* Color development was poor.

† Turbidity in the filtrates on diazotization and coupling was not entirely eliminated.

Sulfathiazole was added to samples of blood serum to obtain final concentrations of 5 to 30 mg. per 100 ml. of blood serum. With dimethyl-alpha-naphthylamine as the coupling reagent the amounts of sulfathiazole recovered varied from 95% to 99% of the theoretical content (average, 97%). The values given in Table 2 are characteristic of several series similarly analyzed.

TABLE 2.—RECOVERY OF SULFATHIAZOLE ADDED TO BLOOD SERUM.

Sulfathiazole in serum, mg. per 100 ml.	Sulfathiazole recovered, mg. per 100 ml.	Per cent recovery.
5.00	4.83	96.5
10.00	9.90	99.0
20.00	19.40	96.9
30.00	28.90	96.4

Procedure of Analysis. Since the recovery of sulfathiazole from serum is within approximately 3% of the theoretical, we have preferred routinely to perform our analyses on serum and to make an arbitrary correction for the loss encountered. The method that we have finally adopted for the analysis of sulfathiazole in serum is essentially an adaptation of the Marshall and Litchfield procedure[7] for the determination of sulfanilamide in whole blood.

Procedure: 2 ml. of serum* obtained from centrifuged clotted blood are run into a 25-ml. volumetric flask containing 10 ml. of 8% trichloracetic acid. After shaking thoroughly to keep the precipitate finally divided, the solution is diluted to the mark with distilled water. The contents are mixed and allowed to stand for 20 minutes; then filtered through Whatman No. 44 paper to obtain a clear, colorless filtrate. Ten milliliters of the filtrate are diazotized at room temperature with 1 ml. of a 0.1% freshly made solution of sodium nitrite. The solution, after standing for 3 minutes, is treated with 1 ml. of an 0.5% solution of ammonium sulfamate†. After mixing thoroughly, 5 ml. of di-methyl-alpha-naphthylamine‡ coupling reagent are added; the tube is stoppered, inverted once, and allowed to stand for 10 minutes.

Comparisons of color development are made by means of a colorimeter (or photoelectric cell device) utilizing sulfathiazole standards of appropriate concentrations carried through the same procedure as with the unknown. It is important that the solutions be well shaken before placing them into the colorimeter cups to eliminate small gas bubbles that may be present. (The gas is presumably nitrogen formed by the destruction of HNO_2 with $NH_2.SO_3.NH_4$). For our purposes we employ a colorimeter (Bausch & Lomb) having an attachable lamp. The eyepiece of the colorimeter is fitted with a No. 74 Wratten filter. Standards of appropriate concentrations are made from a stock solution of sulfathiazole containing 200 mg. per liter. It is convenient to have prepared standards having concentrations of sulfathiazole of 0.2, 0.4 and 0.8 mg. per 100 ml., respectively.

Calculation:

$$\frac{\text{Reading of Standard}}{\text{Reading of Unknown}} \times \text{mg. of sulfathiazole in standard} \times \text{Dilution Factor} \times \text{Correction Factor} = \text{mg. per 100 ml.}$$

Correction factor = 1.03.

Recovery of sulfathiazole from protein-free urine is practically quantitative. The procedure for serum may be applied to urine determinations disregarding the correction factor. It is preferable that appropriate dilutions of urine be made so that sulfathiazole concentration in the diluted urine is between 5 and 30 mg. per 100 ml.

Recovery of Acetylsulfathiazole Added to Whole Blood, Serum, and Normal Urine, Respectively. Acetylsulfathiazole was added to blood, blood serum and urine in concentrations of 5 to 20 mg. per 100 ml., as in experiments with the parent compound. In these determina-

* In blood serum containing high concentrations of sulfathiazole, 1 ml. of serum is employed.

† Marshall and Litchfield[7] recommend that the solution of ammonium sulfamate be buffered with sodium dihydrogen phosphate in order to increase the rate of coupling. In our experience the addition of the buffer has not proved necessary.

‡ Solution contains 1 ml. dimethyl-alpha-naphthylamine in 250 ml. of 95% ethyl alcohol.[6b]

tions 10 ml. of the protein-free filtrate were first heated with 0.5 ml. of 4 N hydrochloric acid in a boiling water bath for 1 hour; then cooled, and the volume readjusted to 10 ml. with distilled water. The procedure followed was the same as that employed in determining the free form, excepting that comparisons were made with standards containing acetylsulfathiazole subjected to hydrolysis instead of sulfathiazole.

When acetylsulfathiazole was added to whole blood the percentage of recoveries in 6 or more duplicate analyses averaged 79%; when added to blood serum, 86%; and to normal urine, 99.6%. The magnitude of the loss in both whole blood and serum would seem to preclude the use of the method for the conjugated form.

The Solubility of Sulfathiazole and Acetylated Sulfathiazole in Phosphate Solutions and in Samples of Buffered Normal Urine at Various Physiologic pH Concentrations. Solubility measurements of sulfathiazole and acetylsulfathiazole were made in dilute phosphate buffer solutions* of pH concentration from 5.6 to 8. An excess of these compounds was suspended in prepared buffer solutions, agitated and kept in a water bath at 38° C. for approximately 2 hours. The solutions were filtered and analyses for total sulfathiazole were made on the filtrates. Since presence of extraneous material may influence the true solubility of a component, similar measurements of solubility were made on urines adjusted to a pH range of 5.6 to 8.

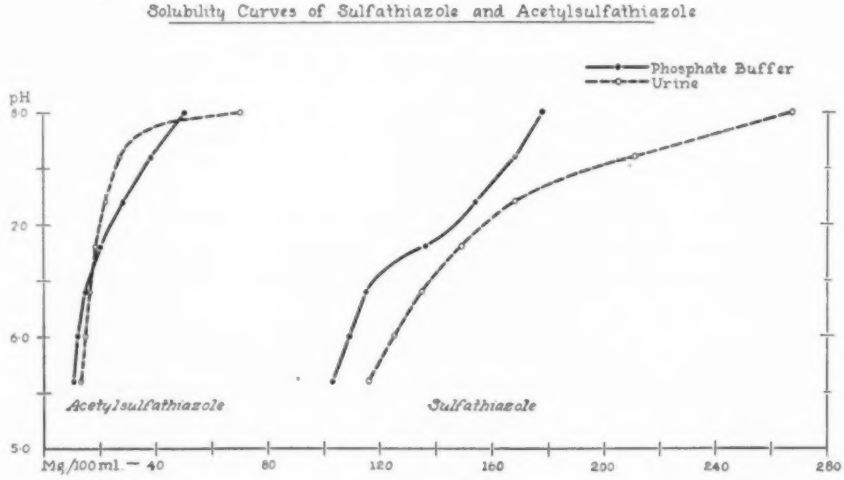

FIG. 1

In Figure 1 the curves are given showing the concentration of sulfathiazole and acetylsulfathiazole in aqueous solutions within the pH range indicated. Each curve represents a composite of three

* The solutions were made by diluting appropriate mixtures of Na_2HPO_4 and KH_2PO_4, 1 part to 10 parts of distilled water.

sets of determinations. It will be seen that the solubility of sulfathiazole in urine and in dilute phosphate solutions does not vary greatly. The same close agreement is observed in the solubility of acetylsulfathiazole in urine and dilute phosphate solutions. Acetylsulfathiazole is shown to be only about one-tenth as soluble as sulfathiazole.

The data concerning the solubility of these compounds support the clinical observations that the occurrence of crystalline concretions in the urine appear to be lessened when the volume of urine is increased by an adequate ingestion of water and its reaction is made alkaline.

The Crystalline Structure of Sulfathiazole and Its Acetyl Derivatives. In our experience the most common type of crystal found in the urine of patients receiving sulfathiazole has been a dumb-bell shaped structure (Fig. 2). Occasionally, rosette and large orthorhombic hemimorphic crystals are also observed.

The dumbbell-shaped crystals vary from 0.005 to 0.02 mm. in diameter. Under the polarizing microscope brush polarizations, similar to those of starch grains, are observed, which suggest that the crystalline structure is not completely formed. The orthorhombic hemimorphic crystals in the urine varied from 0.2 to 0.04 mm. in their largest dimension.

Specimens of urine containing dumbbell-shaped crystals yielded relatively large amounts of the acetyl derivative of sulfathiazole. The crystal structure of acetylated sulfathiazole is shown in Figure 3. These crystals were orthorhombic in structure and consisted of tabular and prismatic forms. The tabular forms were diamond-shaped, the longest diagonal dimension being from 0.01 to 0.05 mm. and the shortest from 0.005 to 0.03 mm. The thickness of the tabular form was approximately one-fifth of the shorter diagonal dimension.

In the prismatic forms the cross-sectional dimensions were approximately the same as those of the tabular forms. The height, however, was approximately two and a half times the shorter diagonal dimension of the cross-section.

Crystals of acetylsulfathiazole prepared by acetylating sulfathiazole with acetic anhydride were the same as those isolated from the urine, excepting that they were approximately two and a half times larger.

Sulfathiazole crystals were suspended in a solution of 0.9% sodium chloride and in normal acid urine. In the salt solution, the crystals appeared as flat pseudohexagonal plates somewhat resembling mica in structure. The dimensions of these crystals ranged from dust particles to a length of 0.3 mm. in the longest axis. Sulfathiazole crystals suspended in urine changed their shape to rectangular tablets. This change in configuration suggests that the crystalline structure of the compound may be polymorphous.

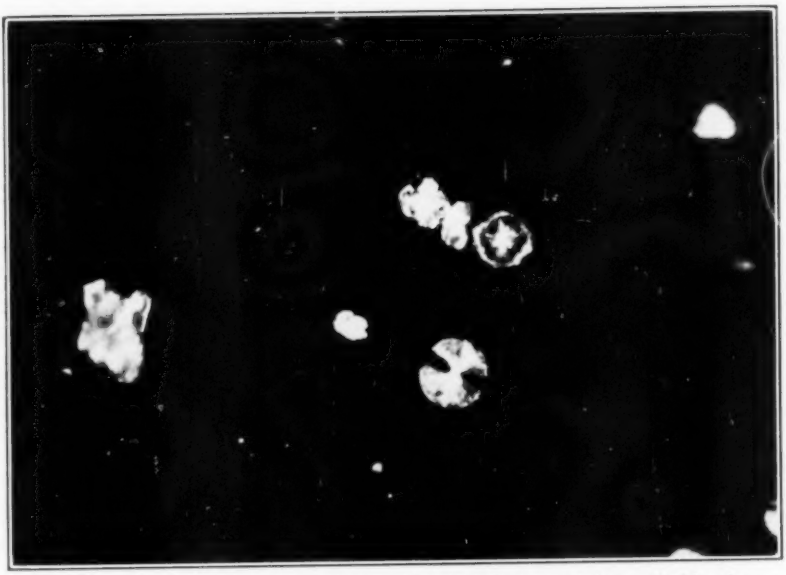

FIG. 2.—Dumb-bell shaped crystal in urine of patients receiving sulfathiazole.

FIG. 3.—Diamond shaped crystal of acetylsulfathiazole.

Recovery and Isolation of Acetylsulfathiazole From the Urines of Individuals Receiving Sulfathiazole. Sediment from the urines of individuals receiving sulfathiazole was separated by centrifugation, pooled and repeatedly washed in water. This pooled, dried, crystalline sediment was heated with 20 cc. of a 1 to 1 mixture of acetone and water, and filtered. The residue on the Fisher-Jones melting point apparatus* melted at 271° to 274° F. The behavior of the material was characteristic; it became hazy before melting and upon melting decomposed, forming a dark brown oil. Under the same conditions the synthetic product, obtained from the acetylation of 2-sulfanilamidothiazole with acetic anhydride, behaved similarly and melted at 272° to 275° F. The melting point of the synthetic acetyl derivative was unaltered by mixing with the product from urine, and the two materials were therefore regarded as identical.

Summary. Applying methods for the analysis of sulfanilamide in whole blood to the measurement of sulfathiazole, we have found that recovery of sulfathiazole in whole blood averages approximately 86% of the theoretical. This diminution in the recovery was shown to occur during protein precipitation. Employing serum instead of whole blood, loss of sulfathiazole is considerably less, averaging only about 3%. For this reason we feel that analysis for sulfathiazole should be made in serum instead of whole blood. A procedure for analysis in serum is suggested in which an arbitrary correction for the loss is made in the final calculation.

Since both sulfathiazole and its acetyl derivative are about twice as soluble in urine of pH 7.6 as in urine of pH 5.6 it may be inferred that when crystalline concentrations owing to sulfathiazole therapy threaten, an effort should be made to keep the urine alkaline and to secure a large urinary volume.

We wish to express our appreciation to Dr. Ralph A. Connor and Messrs. A. W. Postel and W. E. Haesler, Jr., for their aid, and to thank E. R. Squibb & Sons and the Maltbie Chemical Company for supplying us with adequate samples of the compounds.

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* The Fisher-Jones apparatus was used because of the small amount of material required and the desirability of watching the melting under magnification. These melting points are higher than the values (256° to 257°), presumably determined in a capillary tube, which were reported by Fossbinder and Walter.[2] Considering the differences in the apparatus, the high melting point, and the decomposition upon melting, the discrepancy is not surprising. The characteristic behavior of the materials noted above makes this method especially convincing in confirming the identity of the products.

OBJECTIVE ESOPHAGEAL CHANGES DUE TO PSYCHIC FACTORS.

AN ESOPHAGOSCOPIC STUDY WITH REPORT OF 13 CASES.

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THE purpose of this paper is to show that the esophagus undergoes definite changes in response to emotional upsets. These changes can be observed with the esophagoscope, and the relationship between cause and effect positively established. As far as I am aware this has not previously been done.

The patients used in this study represent a cross-section of society from the wealthy to those on relief. Each sought treatment for symptoms that were ascribed to one or more of the organic systems. None of them came to us directly. All were referred, some because of complaints pointing to the esophagus, and others solely because of our interest in making this study.

Our investigative procedure consisted of the usual history and physical examination, essential laboratory tests, and necessary consultations. A detailed social, economic, and emotional history was obtained, recording the patient's worries, fears, apprehensions, difficulties and failures, as well as his hopes, pleasures, and aspirations.

An esophagoscopic examination was made in all cases, using local anesthesia, and noting the presence or absence of esophageal spasm and the size of the lumen. While the esophagoscope was in place, and direct observation possible, the patient was asked to imagine himself in situations which we proposed. These were selected with the aim of bringing forth desirable or undesirable sensations, feelings of security or insecurity. With each proposal or suggestion we noted whether any alteration occurred in the esophagus.

Although some form of fear or sense of inadequacy was a common feature in all these cases, for ease of presentation we have decided to arrange them in groups depending upon whether the difficulties were brought about by marital, social, occupational, or financial insecurity.

GROUP 1.—A twice-married woman, aged 33, an alcoholic, was referred for diagnostic esophagoscopy, because she had been vomiting and expectorating blood, and the possibility of an esophageal varix had arisen.

Except for a traumatically perforated nasal septum with ulceration and markedly dilated nasal vessels, the physical examination was essentially negative.

On the surface she was a mean, cruel, bitter patient. But one could sense that underneath this unpleasant exterior was a sensitive, bewildered person, who did not know where to turn for assistance. She was one of those who acted first and thought afterwards, thereby getting into difficul-

ties and, as a consequence, having to undergo detrimental emotional disturbances. Then instead of adjusting herself to the new situation or extricating herself from it, she expected others to pay for her mistakes, and vented her unhappiness upon any one who was at hand. To fully appreciate the significance of the esophagoscopic findings in her case one must know something more about her personal life and all incidents that might have initiated emotional conflicts.

Coming from a family that believed in the permanency of marriage, she was estranged from her parents by divorcing her first husband, and thereby lost the custody of her boy. Remarriage led to further controversy with her family.

In her second husband she thought she had "a reliable, industrious, kindly, intelligent, well-educated man," but he turned out to be an excessive periodic drinker, who spent his entire pay check for liquor, drove his automobile while intoxicated, and was arrested for this offense on several occasions. And added to this he boasted of his unfaithfulness. At this point of the history she volunteered that she "could go back to her first husband who wanted to remarry her," but this was said so unconvincingly that it appeared she might like to, but could not. They were badly in debt, but she emphasized that she had no desire nor intention of using her previously accumulated resources to meet her financial obligations.

Esophagoscopic Examination. There was no evidence of esophageal varices. But the entire esophagus was spastic and the lumen narrowed to one-half normal size.

While the esophagoscope was in place, she was asked how she "would feel if she had sufficient funds to meet all her obligations." This question brought forth no relaxation of the spasm or alteration in the size of the lumen. The proposal of a vacation elicited a sluggish but only slight relaxation.

The possibility that she might never see her boy again caused instantaneous and complete spasm with absolute closure of the lumen. Whereas, the suggestion that she might have her boy permanently with her brought forth a prompt relaxation of the spasm and a return of the lumen to full normal size, twice as large as was noted at the beginning of the examination.

Then told to imagine how she would feel if suddenly informed that her boy was dead, the esophagus clamped down with lightning speed, the lumen was obliterated, and the muscle quivered. These findings remained several minutes and they were still present when the next question was commenced.

"How would you feel if you got news that your present husband was killed in an automobile accident?" Therewith, the spasm immediately disappeared and the lumen opened widely. At the completion of the esophagoscopy she proffered: "You might as well know. It wouldn't make any difference to me, one way or another, if something happened to my husband."

It will be noted on review of this case that imaginary situations of a personally dreadful or undesired nature led to instantaneous spasm and closure of the esophagus. Thoughts of a pleasant or hoped-for variety caused prompt relaxation and proper widening of the lumen. Problems that were relatively unimportant in her scheme of life elicited correspondingly unimportant changes in the esophagus.

Her daily life presented enough emotional disturbance to account for the spasm and narrowing that were encountered even before the questions were asked.

GROUP 2.—The next 2 cases with esophageal complaints were financially independent bachelors, one aged 59, the other 63. Both were railway men regarded as successes in their respective fields, executive and train dis-

patcher. Overly serious and tense in all that they did, neither knew how to relax, and they got very little fun out of life.

The dispatcher continually dreaded the thought that ultimately he might make a mistake in his work and be responsible for a train wreck. The executive, whose duties called for numerous court appearances and exasperating cross-examinations by staffs of technical lawyers, never got used to testifying and abhorred it.

His medical complaint was pain along the left side of the cervical esophagus. The esophagoscopic examination revealed tremendous spasm of the inferior constrictor of the pharynx at the entrance to the esophagus. Proximal to this there was redness of the mucous membrane from stasis and subsequent infection. In addition, the entire thoracic esophagus was spastic and the lumen narrower than usual.

When the patient was asked to imagine how he would feel if he "could take a long vacation, and get away from both the monotonous routine and the disturbing court sessions," the spasm relaxed and the lumen became wider.

The proposal that he "continue to work under increased irritations and be subject to even more frequent court appearances" brought forth a spasm of the entire esophagus and closure of the lumen. This relaxation and spasm could be elicited consistently and repeatedly in response to desirable and undesirable proposals.

The other patient had symptoms of partial obstruction of the esophagus, restricting his diet to semiliquids. He was sent to us with a tentative diagnosis of hernia of the diaphragm through the esophageal hiatus and secondary pressure upon the lower esophagus.

The esophagoscopic findings were quite similar to those in the previous case, namely, spasm of the entire tube and narrowing of the lumen to one-third normal size. The spasm was particularly marked at the upper and lower sphincters.

When it was suggested that due to an error on his part he might be responsible for a serious train wreck, the spasm increased and the lumen narrowed still further. The proposal that he take a long vacation brought forth relaxation of the spasm and increase in the caliber of the lumen.

After this examination, when the character of the esophageal disturbance had been explained to him, he retired from his tension-producing occupation, bought a chicken ranch, and had no further trouble in swallowing and retaining a regular diet.

These 2 cases are examples of the esophageal spasms that occur in overly serious, conscientious people who lead, tense, straining apprehensive lives without proper intervals of relaxation and recreation. Long continuance of such an unhealthy routine could well enough keep the esophagus in a more or less constant state of spasm.

On the basis of the predominance of the spasm at the upper end in one of the patients and at the lower end in the other, I am inclined to believe that the former would ultimately have developed a cervical esophageal diverticulum and the latter a cardiospasm with attendant dilatation of the lower esophagus.

GROUP 3.—In contrast to the financial status of the 2 previous patients, those in the present group must be classified as social and economic failures, haunted by the fears and uncertainties that attend such insecurity. For their livelihood they had to depend upon government relief, and hence, whenever curtailment of relief threatened, they were stricken with terror, apprehension, and spasm.

Since the problem is an economic one, no amelioration of symptoms should be expected from the use of atropine, tincture of belladonna, sedatives, or other drugs. Improvement and ultimate recovery are to be had only after

the patient has been shown a satisfactory way out of the situation and assisted in finding a new means of livelihood.

A woman, aged 33, recipient of a widowed-mother's pension, was informed that within a few months her daughter would have reached the age where no further state assistance could be allowed. Shortly thereafter her illness began, and she reported to the clinic complaining of "the sensation of a lump in the throat, difficulty in swallowing, and nausea."

Despite the morphine, atropine, and sedatives that were routinely given preliminary to the esophagoscopic examination, we encountered a firmly resistant spasm of the inferior constrictor of the pharynx at the entrance to the esophagus. The balance of the esophagus was also spastic and thickened, and the lumen reduced one-half.

This spasm increased at once when the patient was asked to imagine how she would feel if, in addition to the discontinuance of the pension, her daughter should get married immediately and lend no financial assistance. On the other hand, the suggestion that she might get a son-in-law who would delight in providing the patient with all the necessities and a few of the luxuries of life initiated an immediate esophageal relaxation.

The next patient was a sullen, frustrated, unmarried Greek laborer of 52, a relief recipient, whose complaints were "pains in the chest and cramps in the bowels." He became ill at a time when relief rolls were being reduced and publicity had been given to the fact that the sick would not be stricken from the list. The man had lost all ambition, and his mental and physical responses had become outstandingly sluggish.

Endoscopic examination showed uniform spasm of the entire esophagus. The spasm was aggravated when it was suggested that he might be denied government aid. But, when asked to imagine how he would feel if located in a mountain camp enjoying the fresh mountain air and the smell of the pines, with a cook to supply an abundance of well-prepared food, and not a thing to worry about, there was a lessening of the spasm and a widening of the lumen.

Told to imagine how he would feel if he could get a job paying $500 a month, there was no improvement in the spasm. Apparently he was not interested in anything for which he had to work, or, his imagination was not developed to the point where he could conceive of $500 a month. In order to get an esophageal response I believe it is necessary for the proposed situation to be such that the patient can imagine the possibility of its actually happening.

In the previous cases the esophageal spasms and relaxations occurred immediately after the proper suggestion, but in this patient there was a 45-second delay between suggestion and reaction. It is conceivable that, with his slowed cerebration, each new thought had to await its turn before reaching the consciousness of the preoccupied brain.

Group 4.—There were 2 married men and a married woman in this group, aged 27, 31, and 30 respectively. All 3 were gainfully employed but just barely making ends meet, and, before 1 month was over they had to begin worrying about the oncoming month. They had no lack of imagination, but, on the contrary, set their goals so high that they were unequipped to attain them.

They were selfish, opinionated, and aggressive, as well as easily frightened and discouraged. All 3 attributed their difficulties to marriage, because previously they had had ample incomes and freedom from worry and family responsibility.

The woman's symptoms were poor appetite, frequent headaches, chilly sensations, diarrhea, insomnia, nervousness, dizziness, and pain over the precordia immediately after eating. There was also right upper quadrant pain with a feeling of suction whenever she stooped.

She was referred to us for this study after 3 years of treatment in the neurologic, gynecologic, gastro-enterologic, and otorhinolaryngologic clinics had afforded no relief of symptoms.

Endoscopic examination revealed a uniform spasm of the entire esophagus and a reduction of the lumen to one-third normal size. In addition, there was a small, rapid, continuous, irregular, intermittent, superimposed minor spasm, muscular contraction, or quivering. This looked like what one would expect to see if the heart were exposed during auricular fibrillation; and it also reminded one of the frequency of action of a telegrapher's key during the sending of a message. Nevertheless, this patient's heart action was not disturbed or abnormal in any respect.

I think there is a possibility that these secondary superimposed spasms may be a manifestation of a continuous stream of fresh emotional disturbances engrafting themselves upon the already well-established ones which had caused the major spasm. All the patients in this group had such superimposed spasms.

This patient's esophageal responses to suggestion were similar to those already reported. The major spasm became less marked following pleasant proposals, but showed additional tightening with anxiety situations. The secondary or superimposed spasms ceased when the major spasm relaxed; but they were inconsistent thereafter, sometimes returning with the return of the major spasm, and at other times failing to reappear.

The second patient in this group was referred with the complaints of nausea, vomiting, inability to swallow, and substernal pain. His esophageal spasm was so marked that it was only with the greatest difficulty that the esophagoscope could be introduced. The spasm extended throughout the entire length of the organ, and the grip of the esophageal muscles upon the instrument was so firm that considerable strength was needed in order to withdraw the esophagoscope even a few inches.

Despite this original degree of spasm, the esophagus relaxed fully and instantaneously, and the lumen opened widely when we proposed finding a job for the man and his wife that would be sufficiently remunerative to permit an assured monthly income without worry. The instrument could then be moved up or down with the greatest facility.

A picture of desperate poverty was painted, and the spasm returned. Alternating suggestions of security and insecurity caused alternating relaxation and spasm.

The next patient had also been treated in several departments of the clinic before being transferred for this esophageal study. His symptoms were dizziness, weakness, numbness of the hands, a sensation of fainting, and abdominal pains with nausea.

Esophagoscopic examination showed diffuse uniform spasm of the entire esophagus and reduction of the lumen to one-half normal size. When concrete suggestions of a better job and greater security were presented, the spasm immediately diminished and the lumen widened. When asked to imagine how he would like to have his mother-in-law come to live with him, attempt to regulate his life, and increase his household expenses, the spasm became aggravated and the lumen narrowed to one-fourth normal size.

GROUP 5.—Under this classification come 3 women and a man; 2 were married, 2 single. Their ages ranged from 39 to 64; and in each case there were very definite esophageal symptoms. All had more than a fair measure of financial security, but life had become unbearably monotonous with no prospects of its changing. They had a sense of encirclement, imprisonment, and frustration.

The 4 cases were so much alike that, to avoid repetition, a detailed account will be given in but 1. He was a serious, quiet, unmarried man of 39, the owner of an automobile repair shop, who was doing well in his business

and had an adequate savings account. His education was limited to grammar school. His brothers and sisters had all married and established homes of their own, leaving the aged, deaf mother with him. There was almost no conversation in his life. He ate alone and worked alone. He had no friends, no recreation, and no diversions. Every day was the same as the preceding one.

He was referred to us because of nausea, vomiting, and difficulty in swallowing. Endoscopic examination showed a diffuse uniform spasm of the entire esophagus with narrowing of the lumen. There were no superimposed minor contractions. When he was asked to imagine how he would feel if he could escape from his environment, take a vacation, and get some pleasure out of life, the esophageal spasm relaxed immediately and the lumen widened. The reminder that he might have to continue living as he had been doing caused the spasm to return and the lumen to narrow. A rationalized, balanced scheme of living was arranged for this man, and since that time he has been eating a regular diet without recurrence of symptoms.

An Exception. For 4 years a married woman, aged 31, the mother of 3 children, had complained of blurring vision, spells of dizziness, nervousness, abnormal fatigue, headaches, pain in the right lower quadrant, bloating and abdominal cramps; and during that time she was treated without relief, repeatedly visiting the departments of ophthalmology, internal medicine, proctology, and gastro-enterology. And a few months before we saw her, she had acquired the additional symptoms of difficulty in swallowing, vomiting, and pain with a sense of fullness under the upper end of the sternum.

Her emotional history revealed that she was worried, apprehensive, and insecure financially. She feared that she would not be able to properly clothe and adequately educate her children, and was quite disturbed because of her inability to take a much needed vacation from the monotonous household duties.

Esophagoscopic examination showed a constant, uniform spasm of the entire esophagus and narrowing of the lumen to one-third normal size. Engrafted upon this were the waves of a superimposed intermittent minor spasm.

But suggestions, proposals, and exhortations failed to alter the spasm. There was no relaxation at any time. The possibility of a greater income, a long pleasant vacation, desirable educational facilities, and a new home elicited no response. Unfavorable situations were likewise ineffective in changing the picture.

Had this been the first patient in our study, or had we encountered several of this type at the very start, we would undoubtedly have been led astray in evaluating the influence of suggestions, thoughts, and emotions upon the esophagus. But this case, coming as it did after we had already been thoroughly convinced through our previous studies that the esophagus would respond if the proper subjects had been touched upon, was not hard to understand.

We challenged her story and accused her of having withheld vital information relative to her difficulties. On this point we were very firm, emphasizing that she could not be helped unless she presented her complete problem. This she indicated she would do if the instrument were removed.

Her story confirmed our suspicions. Her overwhelming emotions were regret and remorse. These arose from an irreparable past deed which incited and maintained the uncertainty and fear that as a result she might have to face unpleasant consequences in the future.

Motherless at the age of 5, this girl at 20, while unmarried, became pregnant and had to continue living in a small town where every one knew and saw her. She gave birth to her baby 2 months before the father of

the child could be found and compelled to marry her. The patient's father considered the affair a family disgrace, immediately disowned her, and forced her to move to another city. He died some years after without permitting a reconciliation.

Dreadfully lonesome for an occasional visit with her family, this youngster was denied that privilege by the dictate of her father and the fear of town gossip. There was the added hazard that her son, now grown older, might hear of the incident and learn to hate her. In view of this history it can be seen that we did not ask the proper questions during the esophagoscopic examination and hence failed to get either relaxation or altered spasm.

Summary and Discussion. Twelve cases are reported in which spasm of the entire esophagus was noted and studied by means of the esophagoscope, for the first time as far as I am aware. It was seen that the spasm could be aggravated or relieved, depending upon the type of emotions which were aroused.

All of the patients had a sense of inadequacy, insecurity, or impending trouble. The type of insecurity varied, being either maternal, religious, occupational, social, financial, or marital.

One case is reported in which the spasm was neither relieved nor aggravated by suggestion. This patient later admitted that she had given a false emotional history, but we suspected this at the time of the esophagoscopic examination.

The esophageal reaction and alteration in the spasm is in direct relationship to the personal vitalness of the problem; and, conversely, situations in which the patient has no vital interest are incapable of eliciting an esophageal reflex.

In addition to causing uniform spasm of the esophagus, we believe that disturbing emotional influences are also underlying factors in the production of certain esophageal strictures, cardiospasm, and certain so-called idiopathic pressure diverticula of the esophagus.

Antispasmodics, atropine, tincture of belladonna, and sedatives cannot, in themselves, be expected to afford relief in these patients whose esophageal spasm is brought about by financial insecurity and other serious personal inadequacies. Medicinal therapy alone merely delays proper treatment and allows the condition to progress to an advanced stage.

It goes without saying that all cases with even the slightest esophageal symptoms should be examined by means of the esophagoscope to ascertain the cause of the disorder, and if the trouble is shown to be on an emotional basis the patient should be placed in the hands of a psychiatrist for emotional reëducation, change of mental outlook, and social adjustment.

But it must be clearly understood that no case is to be classified as an emotionally-spastic esophagus and so treated without first positively establishing the diagnosis by esophagoscopic examination, because identical symptoms can occur from stricture, ulcer, carcinoma, and esophageal foreign bodies.

Although the scope of this paper is limited to the esophagus, there is no reason to presume that these spastic emotional effects should be confined solely to this single organ. They undoubtedly occur in all the hollow viscera, including the various ducts, and account for a multitudinous array of symptoms. We have seen 3 cases, at bronchoscopic examination, in which the bronchus alternately widened and tightened in response to favorable and unfavorable suggestions. The significance of these observations in relation to asthma can be readily appreciated.

Conclusions. 1. By means of the esophagoscope we were able to show objectively that disturbing thoughts and emotions produce esophageal spasm.

2. This spasm can be increased and the esophageal lumen narrowed or closed by suggestions that call forth destructive emotions, such as grief, anger, anxiety, apprehension, fear, and spiritual imprisonment.

3. The spasm relaxes and the lumen widens immediately when proposals are made eliciting such emotions as happiness, elation, enthusiasm, contentment, and security.

ROENTGEN RAY THERAPY IN THE TREATMENT OF HERPES ZOSTER.

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Herpes zoster is an extremely painful disease. It is usually not dangerous except when there is involvement of the eye. A variety of treatments has been used, with questionable relief of symptoms; therefore we are presenting this paper on the use of Roentgen ray therapy because of our successful results.

Herpes zoster is a disease due to an irritation of the sensory extramedullary ganglia of the cranial nerves or of the posterior root ganglia of the spinal nerves, which manifests itself by groups of

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vesicles on the skin or mucous membranes along the course of the nerve or nerves involved. The theories of etiology of this disease are numerous.[3,5,9,10,13a,b,15,16] The most widely held today is that it is an inflammatory or irritative process in the ganglion itself from a specific virus or a non-specific invasion such as cancer, leukemia, lues, or an irritation from trauma or drugs such as arsenic. There is some evidence of a close relationship to other virus diseases such as chickenpox.[4,8,14,17] There is confusion in some of these cases reported as herpes zoster because there is no clear differentiation between this and herpes simplex.[4,5,8,10,13a,b,14,17] We will not go into a discussion of the differential diagnosis in this paper. Much work is still to be done, and we hope that with the advancement of knowledge of virus diseases, we shall learn more about the etiology of herpes zoster.

The seriousness of herpes zoster depends not only on the intensity of the symptoms and extent of the vesicles but also on the age of the patient, its location and the unknown factor of individual resistance. The eruption may be preceded or accompanied by pain, burning, itching and tingling. The extent of the vesiculation does not bear a direct relationship to the intensity of these symptoms. The postherpetic syndrome of pain, itching, tingling, burning, and so on, is often the most troublesome part of the disease and may persist for many months.

The treatment has not been as satisfactory as the many different methods would suggest.[1,2,4,6,7,11a,b] It is a self-limited disease which varies greatly in intensity, extent, and severity of the lesions. These facts must be kept in mind when evaluating the effect of any therapy.

For the relief of this syndrome, many things have been tried with varying results: ointments, lotions, heat, administration of such substances as pituitrin,[11a,b] vaccines, arsenic, codeine, and salicylate.

Roentgen ray has been previously used by others, notably Pillsbury,[12] Pendergrast, Kechline,[6] Wood and Knox.* By radiating the spinal ganglion, Kechline in his series of 66 cases showed a diminution of pain and no further development of the cutaneous lesions. His results were best in the early cases. Wood and Knox have had similar experience. Pillsbury used a more superficial therapy over the local lesions and spinal ganglia, and found less effect on the pain than on the eruption. Our findings more nearly parallel Kechline's work.

We also agree with Bailey[1] and Byrnes[2] who recommend that Roentgen ray therapy be used in the postherpetic neuralgias before the more drastic surgical procedures or alcohol injections are employed.

Source of Material. Our entire series of 123 cases of herpes zoster consists of material seen in the medical and dermatological clinics

* F. C. Wood and Leila Knox have kindly supplied us with the data on cases referred to them for treatment by one of us.

of New York Hospital and a few from private practice. There were 72 who received Roentgen ray therapy and 51 who did not. The type of treatment administered was unrelated to the severity of the disease. It depended entirely upon the physician into whose care the patient came. The results of the treatment of the two groups therefore offer a reasonable evaluation of the effectiveness of Roentgen ray therapy. Of the 51 cases in the control group, 14 received injections of pituitrin, others were given sedatives and salves or were merely observed to determine the duration and severity of the disease. There were no recurrent cases in our series.

We became interested in the treatment of herpes zoster because we saw a number of patients disabled by postherpetic pain.

Age, Sex and Race. Chart 1 shows the distribution according to age and sex of the control and treated cases.

CHART 1.—AGE AND SEX.

	Total.	10–20 years.	21–30 years.	31–40 years.	41–50 years.	51–60 years.	61–70 years.	71+ years.
Males . .	48	2	3	6	4	9	13	11
Females . .	75	2	6	8	16	27	11	5
Totals . .	123	4	9	14	20	36	24	16

There were 48 (39%) males and 75 (61%) females. In Kechline's series 90% of the cases were males. In this series 4 (3%) were under 20 years of age, 43 (35%) were between 20 to 50 years and 76 (62%) were over 50 years. This is a much higher per cent of patients over 50 years than is found in the clinic group from which the majority of these patients were taken. Most of the reports in the literature fail to mention the age distribution. Kechline states his cases were 5 to 82 years of age. One of our patients was Japanese and the other 122 were of mixed origin of the white race.

CHART 2.—COMPOSITE CHART OF ALL THE CASES OVER A 6-YEAR PERIOD.

	Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.
No. in groups of 3 mos.	13	10	10	4	9	5	12	3	18	24	4	11
	33			18			33			39		

Seasonal Distribution (Chart 2). The highest individual incidences were in September and October, although on the whole there is very little difference in the groups of 3 months. This lack of seasonal variation corresponds to the observations of others.

Location. The skin lesions of the treated cases showed that the nerve roots were involved in essentially the same distribution as in the series of Kechline's patients: cranial 6, cervical 4, cervical and thoracic 4, thoracic 41, thoracic and lumbar 2, lumbar 15.

Our Present Method of Treatment is to give the patient 200 r daily or every other day, for 5 or 6 treatments, using 200 K.V. through 1 mm. of copper and 1 mm. of aluminum filter at 50 cm. distance in a 6 by 15 portal directly over the spinal root ganglia of the

nerves involved. In some cases treated, a lower total dosage was used because of factors beyond our control.

CHART 3.—RESULTS OF TREATMENT TABULATED ACCORDING TO DURATION OF DISEASE BEFORE FIRST TREATMENT, AND THE AMOUNT OF TREATMENT.

Total Roentgen ray therapy used (expressed in r).	Result.	No. days duration of disease before treatment. 1–3 days.	4–7 days.	8–14 days.	15–28 days.	29+ days.
1 to 400	5 cured	1	3	..	..	1
	0 improved	..	..	..	..	..
	0 failure	..	..	..	..	..
401 to 800	16 cured	7	5	3	1	..
	0 improved	..	..	..	..	..
	2 failures	1	..	..	..	1
801 to 1200	21 cured	4	8	3	1	5
	1 improved	1	..	..	..	..
	6 failures	..	..	1	2	3
1201 to 2400	14 cured	5	6	2	..	1
	3 improved	..	1	1	..	1
	4 failures	2	..	1	..	1
Total No. of patients treated	56 cured	21	23	11	4	13
	4 improved					
	12 failures					

The onset of vesiculation is considered to be the onset of the disease.

Result of Treatment is shown in Chart 3. A study of this chart shows that the largest number of the patients in this series were treated within the first week of the disease. Twenty-one patients had had their symptoms for 1 to 3 days, 23 for 4 to 7 days, 11 for 8 to 14 days, 4 for 15 to 28 days and the remaining 13 had had the herpetic syndrome for over a month. Of this last group, 5 (38%) were failures and 1 was not completely cured.

CHART 4.—TOTAL DURATION BEFORE CURE.

	Control cases. Number.	Control cases. %.	Treated. Number.	Treated. %.
1 to 3 days	0	0	1	2
4 to 7 days	2	4	7	12
8 to 14 days	8	16	26	46
15 to 28 days	8	16	13	23
29 to 60 days	18	35	5	9
2 to 4 months	11	21	2	4
4+ months	4	8	2	4

NOTE.—Table does not include the failures or the incomplete group.

In Chart 4 is analyzed the percentage of cures in relation to the time required. In the cases treated with Roentgen ray 46% were cured within 8 to 14 days, whereas only 16% of the control group was relieved within this period. Furthermore, it required 28 to 60 days to cure 35% in this latter group.

In the Roentgen ray series there were 9 cases who required over 1 month for cure. Of these, only 1 was seen within 30 days of the onset of the disease. This patient received his first treatment on the third day and was given 1800 r. He was relieved of his pain

after 1 month. The other 8 cases were not seen for 1 to 8 months after the onset of symptoms.

CHART 5.—RELATION OF THE TIME OF TREATMENT TO SUCCESS ACHIEVED.

Duration (in days) of disease before treatment.	Cases treated.		Cases cured.	
	Number.	%.	Number.	%.
1 to 7	44	61	39	89
8 to 14	11	15	8	72
15 to 28	4	6	2	50
29+	13	18	7	54

Thirty-nine of the 44 cases (89%) treated in the first 7 days of the disease were completely relieved. Two of the remaining 5 were improved and the other 3 received no benefit from the treatment. Of the 11 treated between the eighth and fourteenth day, there were 8 completely relieved (72%), 2 were partially benefited and 1 was a failure. Of the 4 treated between the fifteenth and twenty-eighth day, 2 (50%) were cured and 2 were failures. Of the 13 treated after the twenty-ninth day, 7 (54%) were cured, 1 was partially benefited, and 5 were completely unrelieved. This analysis shows very conclusively the importance of treating cases of herpes zoster promptly, inasmuch as the cures in the first 7 days were 89%, as compared with only 50% after 14 days.

CHART 6.—FAILURES (12 CASES).

Sex.		Duration before treatment.	Total Roentgen ray therapy (r).	Year treated.	Age in years.			
Male.	Female.				41–50.	51–60.	61–70.	71+
GW		5 mos.	900	1935	..	..	*	
	BD	1 yr.	960	1935	..	*		
	LD	1 day	800	1936	..	*		
	DG	1 mo.	600	1936	..	..	..	*
FD		3 mos.	1600	1937	..	..	..	*
HS		1 mo.	900	1937	..	*		
EM		7 mos.	1050	1937	..	..	*	
	MH	8–14 days	2400	1937	*			
	MS	Pain 2 wks. before erup.; erup. 3 wks.	1200	1937	..	..	*	
DL		3 days	1600	1939	..	..	*	
	FW	2 wks.	2000	1939	..	..	*	
EC		3 days	1600	1939	..	..	..	*
6	6	2 days to 1 yr.	600 to 2400	1935 to 1939	1	3	5	3

There were 6 men and 6 women in the failure group. Chart 4 shows a higher percentage of men when compared to the total number in the series. Eleven of the 12 cases (92%) were in the group over 50 years of age which is higher than the same age distribution (77%) for the entire group. From this it is found that the older group shows a lower percentage of cures than the younger.

The only 2 cases treated before the fourth day of the disease who failed to respond to Roentgen ray therapy have presented interesting problems. They both received a total of less than 2000 r. The first, a man of 74, has been in the hospital for more than

6 months because of his pain and has failed to respond to any of the many therapeutic measures employed. The other, a woman of 60, was placed in the early group because she was treated within 18 hours after the appearance of the vesicles. However, she had complained of severe pain and itching for the previous 2 weeks. The eruption was spreading extensively, but after the second exposure to Roentgen ray the itching ceased and there was no further spread of the vesicles. However, the pain was not alleviated in the least by Roentgen ray therapy, nor by subsequent alcohol injection. She was unable to come in regularly and her total dosage was not as great as we should have preferred. After the end of 3 years she still has the constant pain in the distribution of the original lesions.

Discussion. We have already shown that the success of this treatment is directly dependent on the duration of the disease. We have found repeatedly that treatment has been delayed because the physician has considered the extent of the cutaneous lesion at the onset too insignificant to warrant Roentgen ray treatment. Then, because of persistent pain, he has referred the patient for treatment after the optimal date for relief has passed.

We have observed that the symptoms may be exaggerated after the first treatment. It is therefore important to warn patients of this reaction and advise them that improvement will follow subsequent treatments.

There is a tendency for patients to desist from Roentgen therapy after a few treatments because of the relief from pain and because the local lesions do not show further spread. It is important to insist on the full course. Although some may respond to smaller doses, we have found it wise to give the total of 1000 to 1200 r because, after a brief interval in an occasional one of our insufficiently treated cases, there has been a recurrence of the pain and parathesias which were relieved by further treatment.

Conclusion. From this study of 72 cases of herpes zoster we believe that Roentgen therapy is an ideal agent for the relief of herpetic syndrome and that better results will ensue if adequate treatment is started early.

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BLOOD STUDIES IN MALARIA.

THE GENESIS OF BLOOD CELLS IN RELATION TO TREATMENT WITH QUININE.

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BLOOD studies in malaria in relation to treatment were limited to those concerned with the rate of production of hemoglobin and erythrocytes until investigations concerning the regeneration of blood in pernicious anemia after treatment with liver led to similar studies in malaria. Davidson and McCrie[3] found that the degree of reticulation in malaria was proportional to the degree of anemia and to the ability of the bone marrow to respond to it. Yang and Berglund[20] observed an increase of reticulocytes and eosinophils during the treatment of a case of tertian malaria with quinine bisulphate. Benhamou[1] obtained reticulocytoses as high as 19% in the course of the anemia due to malaria, but did not make clear the relationship to treatment. Eight days after treatment with quinine was started Farley[4] obtained reticulocytoses as high as 37% in monkeys (*Macaca mulatta*) infected with *Plasmodium knowlesi*. He also obtained persistent submaximal reticulocytoses in the instances in which treatment resulted in chronic infections with only a few parasites in circulation. He and Bromfield[5] found very little increase of the reticulocytes in experimental human infections, in spite of the anemia, but obtained counts in the natural human infections which ranged from 0.6% to 10.9%. They observed reticulocytoses consistently after treatment, and found that the intensity of response was dependent on the degree of anemia, and that the maximum reticulocytosis averaged 29% and occurred 6 to 10 days after treatment had been started. They concluded that an increased production of red cells followed the destruction of parasites, and was quite independent of the administration of hematinics. Menon, Krishnaswamy and Anamalai[12] found an average reticulocyte count of 1.06% in 10 cases of acute malaria and of 3.55% in 7 cases of chronic malaria. They obtained a rise in count following treatment with quinine. Pokrowski[15] reported a reticulocyte count of 1% in a case of tertian malaria, and of 0.2 to 10.6% in cases of chronic estivo-autumnal malaria. Studies of the bone marrow were made in the latter cases and the per cent of reticulated erythrocytes was found to vary between 0.8 and 3.7. Malamos[10] studied the blood of monkeys (*Macacus rhesus*) inoculated with malaria and obtained reticulocyte counts varying from 0.1% to

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3.5% in infections with *Plasmodium knowlesi*, and from 0.7% to 2% in infections with *Plasmodium cynomolgi*. In 2 cases of infection with *Plasmodium vivax* Kitchen[7] found an elevation of reticulocytes to 100,000 cells per mm.^{3} on the fifteenth and twenty-second days of the infection, respectively, and continuance at that level until the fifty-fourth and fiftieth days.

It is obvious from these studies that, while regeneration of red cells is more or less active in malaria *per se*, it is definitely stimulated to greater activity incident to treatment and removal of the parasites from the blood. There are few reports, on the other hand, concerning the effects of the same factors upon the white cells.

Bunker[2] studied the blood of 10 paretics during paroxysms in the course of therapeutic infections with tertian malaria. In 9 of the cases he found that a decrease of the white count always occurred during the period of rising temperature and was followed by a leukocytosis 2 to 4 hours later in 77% of the paroxysms studied. He considered that the leukocytoses were analogous to the effects of intravenous injection of foreign protein. Ross and Thompson[16] observed leukopenias ranging from 300 to 2000 cells per mm.^{3} during the paroxysms of malaria. The white counts increased coincident with subsidence of fever and disappearance of asexual forms of the parasites, following treatment with quinine. Counts of 20,000 to 30,000 were obtained, but not maintained, about 7 days after treatment was started. The authors believe that the high counts were related to the large amounts of quinine present in the system at the time.

The leukocytic picture following administration of quinine in malaria cannot be adequately evaluated without consideration of the effect of quinine upon the leukocytes of normal individuals. The benzene ring is a component of various substances which cause chemical agranulocytosis. Quinine contains that ring and is listed among the drugs which cause agranulocytosis in man. It has been blamed as the causative agent in various clinical conditions in which quinine was a part of the therapy and in which agranulocytosis developed during the course of treatment. In their handbook of hematology, Kracke and Garver[8] state that quinine has been "suspected" of causing suppression of the leukocytes in some instances. Groen and Gelderman[6] reported a case in which fever and the complaint of headache and pain in the neck, accompanied by progressive leukopenia, followed the administration of sodium salicylate and quinine. Four days before death the white count decreased to only 1444 cells per mm.^{3} with 12% neutrophils, and necrotic angina ensued. Norris[13] reported the case of a patient who took quinine to control fever before coming under observation and to whom 20 gr. of pyramidon were given 2 days before the first blood count was made. The total white count was found to be only 150 cells per mm.^{3} with a complete suppression of the granulocytes. Norris also

observed several cases of malaria in which death occurred during treatment with quinine after parasites had disappeared from the blood, and he suspected that the deaths were due to agranulocytosis caused by the quinine.

It is only in the case reported by Vitug, Chavez and Austria,[19] however, that a causal relationship of quinine to agranulocytosis seems definitely justified. The patient had been taking 1.2 gm. of quinine bisulphate daily. She developed a progressive leukopenia which by the seventh day of treatment had decreased to a level of only 700 cells per mm.^{3} with 1% granulocytes. The quinine was discontinued and a blood transfusion was given. The white count returned to normal. After recovery, a second course of treatment with quinine was started in doses of 0.9 gm. daily. Four days later reductions of the granulocytes again occurred. The quinine was discontinued and the white count once more returned to normal.

Hematopoietic sensitization to quinine seems to be proven only in relation to the platelets. Peshkin and Miller[14] reported the case of an individual in whom an allergic status was established by injection of quinine and who developed thrombocytopenia, positive skin reaction and passive transfer reaction when subjected to a levorotatory group of chinchona compounds. They also cited a case reported by Maritschek and Markowitz[11] in whom 0.3 gm. of quinine produced severe thrombocytopenia with purpura and hemorrhages 15 years after the patient had suffered from quinine poisoning.

Reports based on experimental administration of quinine are few and contradictory. Vincent[18] found a diminution of the total leukocytes following injections of quinine in rabbits and guinea pigs with an immobilization of the white blood cells after large doses. In the human he observed a diminution of the white count 1 to 17 hours after quinine was taken by mouth. Lewetayer[9] concluded that subcutaneous injection of quinine chloride in the horse provoked an increase in the circulating neutrophils, but his figures are not significant. Roth[17] obtained lymphocytoses for several hours after administration of quinine in normal humans, but no significant effect was noted upon the granulocytes. The lymphocytoses, however, were succeeded by lymphopenias which were accompanied by an increase in the granulocytes. These observations were made during the first 24-hour period after administration of single doses of quinine. Roth also studied the effects of prolonged administration of quinine to dogs, and found that this resulted in a reduction of eosinophils and of lymphocytes and in an increase of granulocytes with death on the fifteenth day.

While these various reports indicate that both quinine itself and the treatment of malaria by the drug elicit definite modifications in the different strains of blood cells, they are for the most part limited to observations upon only one strain at a time, and are consequently uncorrelated. The studies to be reported were there-

fore undertaken in order to correlate counts of both the red and the white cells with treatment and with the progress of the malarial infections, so as to determine any interdependence which may exist between these factors.

This presentation is based on data obtained during a preliminary survey in 1935. Since it has been impossible to continue the work as planned and the data obtained are consistent in each case and represent a correlation not previously reported, it seems indicated to present it. The data are assembled from counts of the reticulocytes, erythrocytes and leukocytes made during the treatment of 4 patients[2]* with estivo-autumnal malaria.

Material and Methods. The first erythrocyte count of each patient is taken from the routine hospital record made at the time of admission. The remainder of the counts were made as follows: The tip of the finger was punctured so that it bled without squeezing. The first 2 drops were discarded. Thomas pipettes were used for both the red and the white counts. The dilution for the white counts was 1 to 50, and for the red counts 1 to 400. The counts were made in duplicate on both sides of the counting chamber. When leukopenia was present, the white counts were repeated within 1 to 4 hours of each other, and an average of the two counts is used for the records. Two to 500 cells were included in the differential counts, which were made on specimen slide smears. Until the eighth day of treatment, only reticulocyte counts were made. After that, complete blood examinations were made daily.

The reticulocytes were counted in wet smears stained with brilliant cresyl blue. The per cent was obtained on the basis of the number met in a count of from 2000 to 5000 red cells. The number per mm.^{3} was computed on the basis of the percentage of the total red cell count.

The 4 patients who served for these studies were sisters with coincident infections with estivo-autumnal malaria. Myrtis (Case 1) was admitted in a state of coma. The other 3 sisters were admitted 3 days later because they were found to have malarial parasites in the blood. All had been sleeping in the same room, which was inadequately screened. It is presumed that all 4 were infected with the same strain of parasites.

The treatment given during the periods of observation is indicated in the charts of experimental data. The diet was soft. The children were all undernourished and anemic; Myrtis and Mary (Cases 1 and 2) more so than the other 2. Any other relevant clinical material is given in the following brief case abstracts.

Clinical Notes. Case 1.—(Charts 1 and 1*A*.) Myrtis L., aged 8 years, was admitted in coma. While under treatment the temperature was remittent and intermittent for 7 days. The maxima varied from 100° to 105° F.

Case 2.—(Charts 2 and 2*A*.) Mary L., aged 11 years, history of chills and fever. The temperature was irregularly intermittent. The maximum was 102° F. It returned to normal 8 days after treatment was started.

Case 3.—(Charts 3 and 3*A*.) Nellie L., aged 4 years, history of chills and fever. During the first 4 days of treatment the fever was remittent, reaching a maximum of 102° F. It became normal on the fifth day.

Case 4.—(Charts 4 and 4*A*.) Elinor L., aged 7 years, history of chills and fever. The temperature was remittent around 100° F. during the first 4 days of treatment.

* Dr. Claude McK. Burpee, Professor of Pediatrics, Georgia University School of Medicine, kindly permitted the study of these patients.

Results. The relationships brought out by the counts can best be observed by reference to the charts. A reticulocytosis followed the regression of the fever and the disappearance of the asexual forms of the parasites from the circulation. It was coincident with the appearance of numerous gametes. On the third day after treatment was begun the reticulocytes ranged from 0.1% to 3.5%, or about 4000 to 100,000 mm^3. The number was definitely increased by the eighth day after treatment in all but Case 1. In that case the percentage was still only 0.1% on the sixth day after treatment was started but rose to 7% 5 days later, or 4 days after the temperature reached normal. The peak of the reticulocytosis occurred on an average 11 days after the start of treatment. The reticulocytes remained elevated at levels between 400,000 and 600,000 per mm.^{3} for 7 to 9 days after the peak was attained. They then began to fall abruptly on an average of the nineteenth day from the start of treatment.

The erythrocytes were microcytic at the time of admission. They decreased progressively in number from the beginning of treatment until an average of 11 days thereafter, at which time they had fallen to their lowest levels. By that time the reticulocytes had increased to their peak. Numerous crescent bodies were present in the dry smears during the period of reticulocytosis, and were probably representative of ruptured erythrocytes. The total red count remained depressed to an average level of 2,500,000 per mm.^{3} during the period at which the reticulocytes remained stationary at a peak. After the reticulocyte count began to decrease on about the nineteenth day from the beginning of treatment, the red counts progressively increased and normal-sized erythrocytes began to appear.

The leukocytes ranged from 7000 to 16,000 per mm.^{3} until about the eleventh day of treatment. At about that time, which was the period of greatest increase in reticulocytes and greatest decrease in erythrocytes, the leukocytes began to decrease. The decrease was largely at the expense of the neutrophils and continued progressively throughout the period of reticulocytosis. The lowest levels usually occurred within a day preceding or following the time that the reticulocyte counts began to decrease to normal. From that time the neutrophils increased progressively, and this progressive increase was accompanied by a marked eosinophilia.

LEGENDS FOR CHARTS 1 TO 4 AND CHARTS 1*A* TO 4*A*.

CHARTS 1 to 4.—(Cases 1 to 4.) Total red and white counts; percentage of reticulocytes; absolute number of reticulated and non-reticulated erythrocytes; treatment.

CHARTS 1*A* to 4*A*.—(Cases 1 to 4.) Total white counts and absolute number of the different white blood cells during the period of treatment.

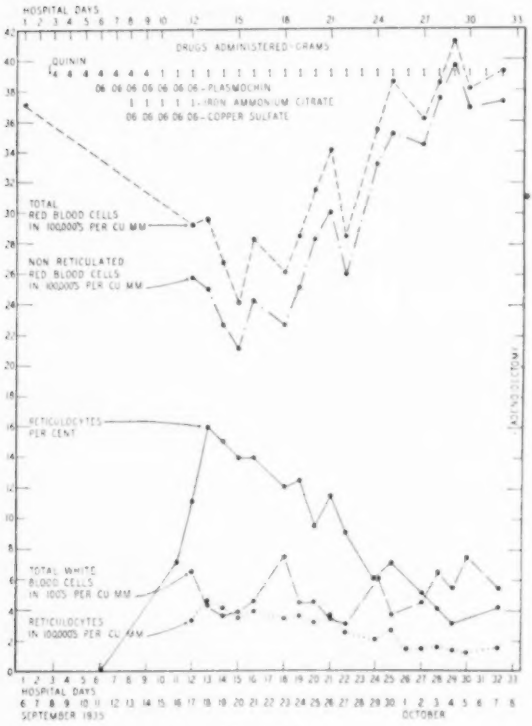

CHART 1.

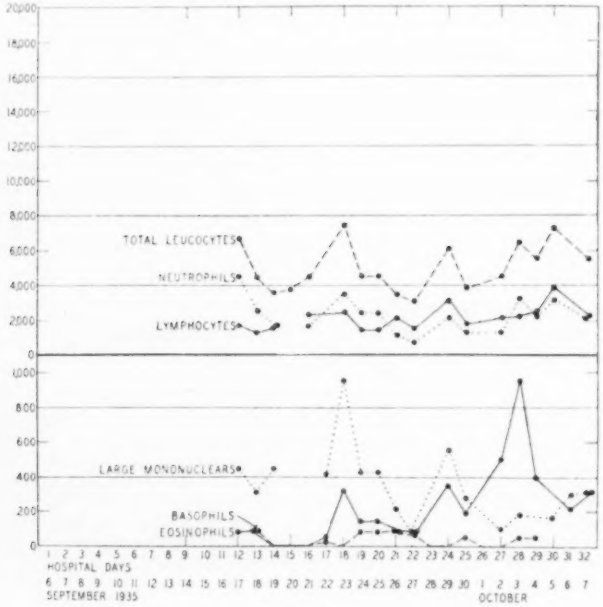

CHART 1A.

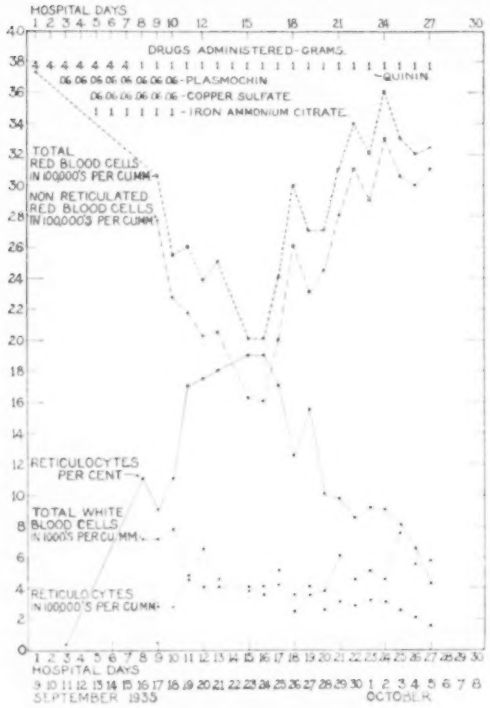

CHART 2.

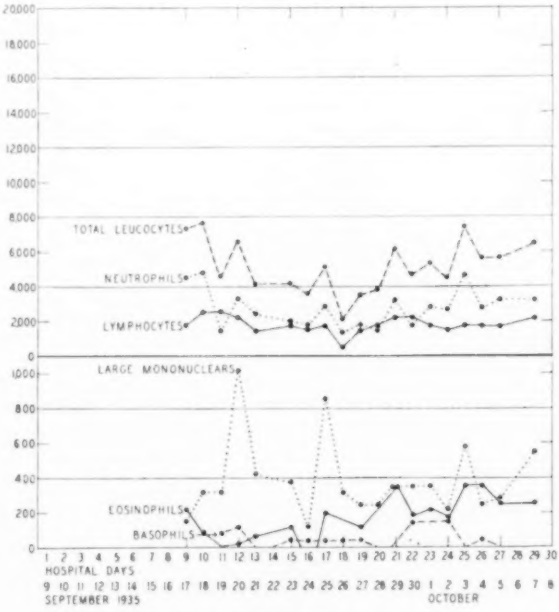

CHART 2A

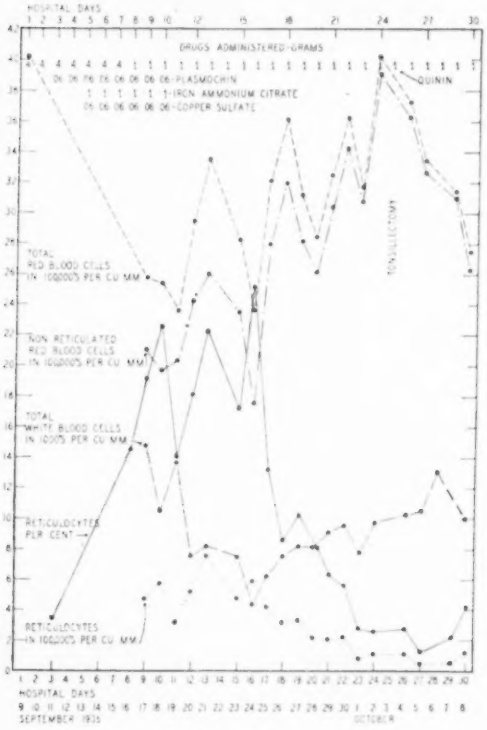
HOSPITAL DAYS
DRUGS ADMINISTERED-GRAMS
0.6 PLASMOCHIN
1 IRON AMMONIUM CITRATE
0.06 COPPER SULFATE
QUININ
TOTAL RED BLOOD CELLS IN 1000005 PER CU MM
IRON RETICULATED RED BLOOD CELLS IN 1000005 PER CU MM
TOTAL WHITE BLOOD CELLS IN 1000S PER CU MM
RETICULOCYTES PER CENT
RETICULOCYTES IN 1000005 PER CU MM
HOSPITAL DAYS
SEPTEMBER 1935
OCTOBER

CHART 3.

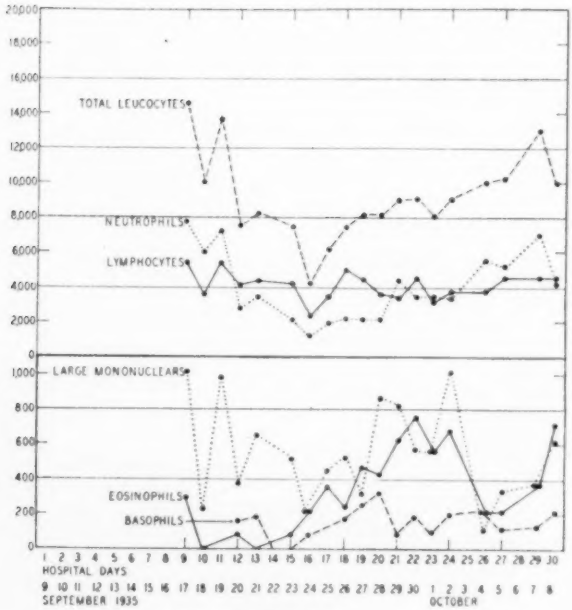

CHART 3A.

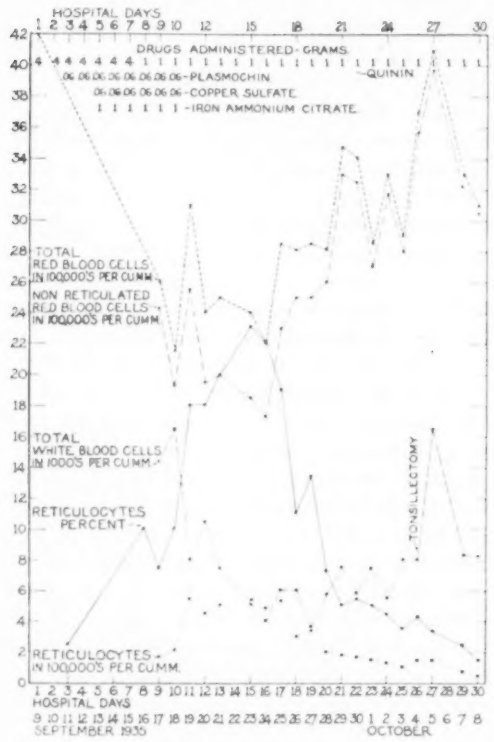

CHART 4.

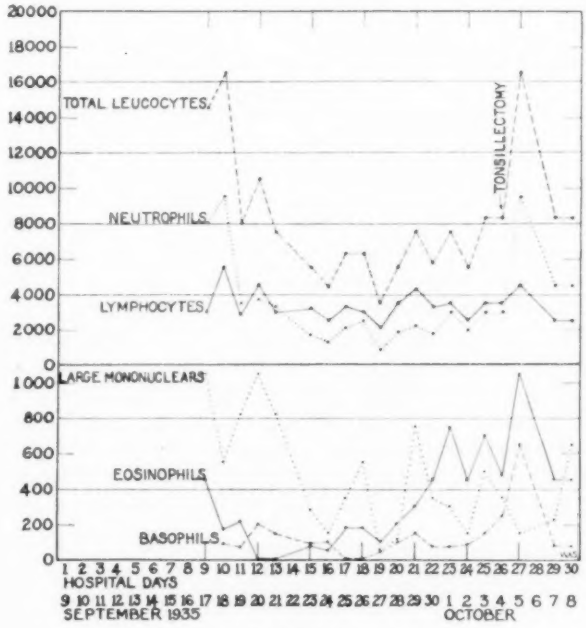

CHART 4A.

The lymphocytes remained stationary throughout the periods of observation. In the 2 younger sisters (Cases 3 and 4) the counts were about 4000 per mm.^{3}, and in the 2 older sisters (Cases 1 and 2) about 2000 mm^3. The differences in the minimal total white counts in the 4 cases at the periods of leukopenia are dependent mainly on the lymphocytic levels in each case.

Basophils were uniformly present during the period of observation. They varied from 40 to 400 per mm.^{3}, and their presence in the smears in such numbers was most striking during the periods of leukopenia.

The number of large mononuclear cells varied from day to day without respect to the clinical status and followed no definite curve.

Discussion. Data obtained from other patients, both children and adults, admitted early in the course of malaria and in a state of good nutrition, indicate more rapid regeneration of the red cells after beginning treatment with quinine than occurred in these 4 cases, more rapid return of the erythrocytes to normal, and frequently leukocytoses subsequent to brief period of leukopenia. Since these are quantitative rather than qualitative differences from the findings in the patients reported here, it seems probable that the prolongation of the various stages in hematopoietic activity in these children is related to the degree of cachexia and is a reflection merely of a more sluggish marrow secondary to it. The prolongation itself has served to permit of enough observations at each stage of recovery to bring out the salient points of that stage.

Obviously in these cases, the regeneration of red cells, as indicated by the appearance of reticulocytes, followed the subsidence of fever and the disappearance of asexual forms of parasites, incident to treatment with quinine. That the regeneration was due to the quinine *per se* is unlikely. That it was due indirectly to the quinine, however, by virtue of the depressant effect of the drug upon the parasites and the consequent removal of toxic factors caused by the parasites, seems likely.

That the white count should decrease during the period of most active formation of reticulocytes, and again increase when reticulocytosis subsides, seems to be directly related to the genesis of blood cells and not due to quinine. This is particularly likely in view of the experiments of Roth with dogs, and in view of the fact that treatment with quinine was continued well past the period of leukopenia. Since the changes in the granulocytic counts are so definitely related to those of the reticulocytes, and since the return of the granulocytes to the circulation is associated with development of an eosinophilia, it seems that the granulopenia must be a phenomenon in the genesis of blood cells in the bone marrow.

Summary and Conclusions. Data related to hematopoietic regeneration are correlated from total and differential counts of the

erythrocytes, reticulocytes, and white cells, which were made throughout the course of treatment with quinine of 4 sisters with estivo-autumnal malaria.

A definite sequence is found in the regeneration of the elements formed in the bone marrow, *viz:* reticulocytes, erythrocytes, neutrophils, eosinophils. The lymphocytes, basophils and large mononuclear cells were unaffected.

A reticulocytosis followed defervescence and the disappearance of asexual forms of parasites, and it was synchronous with the appearance of gametes. The number of reticulocytes was increased by the eighth day of treatment, reached a peak by the eleventh day, remained at a plateau until the nineteenth day, and then began to fall.

The number of erythrocytes had begun to fall by the eighth day of treatment, that is, when the reticulocytes were definitely rising. They continued to decrease to low levels until the nineteenth day of treatment, that is, until the time that the reticulocytes began to fall.

The number of leukocytes remained stationary at normal levels until the twelfth day of treatment, that is, until the reticulocytes reached a peak. They then began to progressively decrease until the nineteenth day of treatment, that is, until the reticulocytes began to decrease. At that time they began to return to normal, accompanied by an eosinophilia. The changes in the leukocyte counts were due to changes in the neutrophils.

The temporary granulopenia is considered probably a genetic phenomenon because of its relationship to the changes in the reticulocytes and to the total red cells, and because of the development of an eosinophilia at its cessation.

The author wishes to thank Dr. Edna H. Tompkins, Department of Anatomy, Vanderbilt University School of Medicine, for help in compiling this report.

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MAINTENANCE OF THE SEDIMENTATION RATE OF ERYTHROCYTES IN VITRO IN CASES OF MALIGNANT TUMORS AND HODGKIN'S DISEASE.

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It has been shown by numerous investigators that the sedimentation rate of erythrocytes in blood that is left standing at room temperature begins to decline after the first few hours and reaches extremely low, at times hardly readable, values at the end of 24 hours.[2b]

No exceptions to this were noted until recently, when Koster[3a] reported that in certain specimens of blood the sedimentation rate remains the same throughout the 24 hours and that in others it may even become accelerated significantly within the first 6 hours, or progressively throughout the 24-hour period. Such exceptional changes in the sedimentation rates of erythrocytes he found only in the bloods of patients who have malignant tumors or Hodgkin's disease, or who have been given certain drugs, such as potassium iodide, bismuth, salvarsan, aminopyrine, lipiodol, perabrodil, oral tetragnost, and, as we have since found, also sulphanilamide and sulphapyridine.

When Koster applied the results of this observation to the study of serial sedimentation rates of erythrocytes in the diagnosis of malignant tumors, he found the results to be 95% positive (*i. e.*, rate maintained) in 112 cases of malignant tumors, and 100% in 14 cases of Hodgkin's disease. In 100 normal persons and in 460 pathologic but non-malignant conditions, the sedimentation rate declined essentially in accordance with previous observations.

Since any aid in diagnosis of malignant tumors is to be welcomed, especially if that aid is a simple procedure which can be carried out by any medical practitioner, it was deemed worth while to repeat Koster's work.

Method. The technique employed was as follows: 8 cc. of venous blood were mixed with 2 cc. of freshly prepared 3.8% sodium citrate in a graduated test tube. This constituted the store of blood from which Wintrobe sedimentation tubes were filled directly after the blood was drawn, then after 1, 2, 3, 4, 5, 6 hours, and finally after 24 hours. The blood was thoroughly mixed each time before removing specimens for sedimentation tests, since the red cells settle out between tests. The temperature of the room where the blood was kept and the tests carried out was fairly constant. All the readings were made exactly 1 hour from the time of filling the sedimentation tube. The sedimentation tubes were carefully cleaned and dried before use. Many tests were set up in duplicate and triplicate, especially in those bloods which had a slow sedimentation rate. The greatest variation in readings seldom exceeded 2 mm. This is in agreement with the results of Ham and Curtis[2a] on duplicate determinations.

It should be noted that our technique is essentially that of Koster, except for the difference in the mixing of the blood, and in the use of the Wintrobe instead of the Westergren tube. These changes in no way affected the results. Sample data obtained with this method are given in Table 1.

TABLE 1.—SERIAL SEDIMENTATION RATES IN STORED CITRATED BLOOD.

Diagnosis.	Directly after blood is drawn.	After 1 hour.	After 2 hours.	After 3 hours.	After 4 hours.	After 5 hours.	After 6 hours.	After 24 hours.
Normal individual	8	8	7	7	6	3	2	1
Diabetes mellitus	25	25	24	24	20	16	12	3
Carcinoma of stomach	11	11	10	11	11	12	12	13
Carcinoma of lung	65	64	64	65	64	64	65	63
Carcinoma of esophagus	38	39	44	43	35	35	26	18
Hodgkin's disease	60	61	60	64	62	62	61	59

Materials. Patients in the medical and surgical wards of this hospital constituted the majority of cases which furnished the blood for the sedimentation tests. A few cases from the out-patient department, as well as several from private sources, are included in this series. Only a few with obvious malignant disease were selected for testing. The rest, for the most part, were routine admissions, some of which presented problems in differential diagnosis where either a malignant tumor or Hodgkin's disease was also considered. Particular care was taken to exclude any case from the records in which the administration of drugs might have influenced the result of the tests.

Whenever a *positive* sedimentation curve was obtained in a patient, *i. e.*, one which could be interpreted as denoting a malignant tumor or Hodgkin's disease, the diagnosis was confirmed either by surgery, biopsy or autopsy. Only a few cases with negative sedimentation curves could be followed up in such a manner because the majority of them improved clinically.

In this manner serial sedimentation tests were done for a period of $2\frac{1}{2}$ years.

Results. Data on 176 cases are presented. The important facts are arranged in Table 2.

TABLE 2.—DIAGNOSTIC ACCURACY OF SERIAL SEDIMENTATION CURVES.

	Number.	With positive sedim. curve.	With negative sedim. curve.	Percentage accuracy.
Proven malignant cases	118	113	5	95.7
Proven cases of Hodgkin's disease	3	3	0	100.0
Non-malignant cases	55	3	52	94.6
Total	176			

Of the 5 cases of malignancy with the negative sedimentation curves or false negatives, 1 was a carcinoma of the lung, 3 were carcinomas of the stomach and 1 was a carcinoma of the transverse colon. In 2 of these cases the sedimentation studies were done twice and both times yielded essentially the same results.

Concerning the 3 non-malignant cases with positive curves, or false positives, where drug effects could be more or less definitely eliminated, one was an elderly woman with hypertrophic arthritis and moderately severe anemia. The second was also an elderly woman with pernicious anemia, who came to the hospital in a very debilitated state, but responded subsequently to liver therapy with much improvement. The third was a luetic woman with a clinical picture of carcinoma of the stomach, which, however, was not confirmed by operation and autopsy.

The further courses of the first 2 cases are being followed with much interest.

From the numerous cases in which the serial sedimentation test coincided with the pathologic diagnosis, but was at variance with the clinical diagnosis, a few records are given:

CASE 1.—C. F., aged 73 years, male, admitted on August 2, 1938, complaining of increasing jaundice and pruritus, chilly sensations, epigastric pain and anorexia for the past 8 days; and clay-colored stools and vomiting for the preceding 6 days. The jaundice and pruritus had increased markedly 24 hours before admission.

Past history was negative except for an attack of weakness and palpitation about 8 years ago. The family history revealed the interesting fact that in 1935 a son of this patient had died of a cancer of the pancreas after an operation.

Physical examination on admission: temperature 100.2°, pulse 70, respirations 24 per minute, blood pressure 150/74 mm. of mercury. The scleræ and skin were deeply jaundiced. Excoriations were visible all over the body but were especially numerous over the anal cleft. The thorax was emphysematous and the lungs hyperresonant. A faint systolic blow was heard near the apex of the heart. There was slight muscle spasm in the right upper abdominal quadrant with tenderness maximal in the midclavicular line 3 finger-breadths below the costal margin. The edge was irregular and felt firm but slightly tender. A globular, fairly firm, but fluctuant mass the size of an egg was felt 3 finger-breadths below the costal margin just beyond the midclavicular line. This mass seemed somewhat distinct from the liver, was tender and moved with respiration. Both legs showed varicose veins. The peripheral arteries were sclerotic. The prostate gland was moderately enlarged, soft, and slightly irregular.

Laboratory Data. Bile was found in the urine, but not in the stool; icterus index rose in 2 days from 71 to 189 units; total cholesterol, 133 mg. per 100 cc. blood; cholesterol esters, 51%; phosphatase, 16.5 units; nonprotein nitrogen, 44 mg. per 100 cc. blood; total proteins, 6.66 gm. per 100 cc. blood, with an A/G ratio of 0.90.

Course. Direct Roentgen ray study of the gall bladder revealed no evidence of calculi. After the oral administration of iodeikon, the gall bladder failed to visualize. The finding was indicative of a hepatic or biliary lesion. The clinical impression of the case was that of a carcinoma of the head of the pancreas. On August 8, 1938, a serial erythrocyte sedimentation curve was interpreted to mean that there was no malignancy present. Jaundice was increasing steadily. An exploratory operation followed by a cholecystostomy was done on August 13. The gall bladder was found to be distended to the size of a lemon, tense, but free of calculi. The common duct was distended, and again no stone was felt. No masses were palpated in the pancreas. The gall bladder was drained and a probe passed from

the cystic duct into a distended common bile duct, which could not get through into the duodenum.

Although the immediate postoperative condition of the patient was good, on the night of August 15 his pulse became irregular, coarse râles appeared at the base of the right lung. His condition became poor, the fibrillation persisted, and he expired on the morning of August 17. The postmortem diagnosis was: chronic interstitial pancreatitis with fibrosis; stenosis of common bile duct; arteriosclerotic heart disease.

Comment. In this case the clinical impression of a malignant growth had much in its favor; but the serial sedimentation curve pointed in the direction of the correct diagnosis.

CASE 2.—L. W., aged 40 years, female, colored, first came to the O.P.D. of this hospital in 1937, complaining of polyuria and loss of weight. On investigation, she was found to have diabetes mellitus and also a positive Wassermann reaction. Her diabetes had been treated with diet and insulin. She received several courses of antiluetic therapy. In May, 1937, a spinal fluid Wassermann was negative.

She was admitted to another hospital in April, 1938, complaining of a cough that had lasted 3 weeks. The blood pressure at that time was 190/120. The diagnosis was left pleural effusion, etiology unknown. Investigation for tuberculosis, including guinea pig inoculation, was negative. A diagnosis of diabetes mellitus and fibromyomata uteri was also made. She was discharged from the hospital after 1 month.

In June, 1938, she was admitted to a second hospital for similar complaints. The diagnosis was left hydropneumothorax, diabetes mellitus and fibromyomata uteri. Investigation for tuberculosis was negative.

In August, 1938, she was admitted to this hospital with the complaint of dyspnea on effort and cough. She was found to have a left pleural effusion. This was tapped several times. Repeated investigation and guinea pig inoculations were all negative for tuberculosis.

On August 24, the serial erythrocyte sedimentation test (Koster) was positive for malignancy. On September 9, a thoracoscopy was done. This revealed an area of granulation tissue on the posterior parietal wall surrounded by some small hemorrhagic cyst-like areas. No diagnosis was warranted from this evidence. The opinion that the pleural effusion and the fibromyomata might be linked together as in Meigs' syndrome was strongly entertained and a hysterectomy was performed. After all these procedures, the patient was discharged markedly improved in her general condition.

For 7 months thereafter she got along quite well. On May 20, 1939, she was readmitted to this hospital with complaints of dyspnea, pains in various joints of the body and pain in the chest. There was no cough or bloody sputum.

Physical Examination. Temperature 101, pulse 92, and respirations 22 per minute, blood pressure 140/90 mm. of mercury. She was slightly dyspneic. The fundi showed fairly advanced sclerosis of vessels. Several patches of exudate and a few recent hemorrhages were seen in both fundi. The disks were normal. The throat was moderately congested. The tonsils showed evidence of chronic inflammation. There was poor oral hygiene. The tongue was coated and teeth carious. The thorax revealed a diminution in mobility of the left side. There were râles at the right base. In the left chest there was absent tactile fremitus anteriorly and posteriorly almost up to the apex, dullness to flatness to percussion, and absent breath sounds. The left border of the heart could not be made out due to flatness of the left chest. The right border was about 6 cm. to the right of the sternum. The heart rate was rapid, with a gallop rhythm. A to-and-fro

friction rub was heard best at the base of the sternum. No murmurs could be made out. The abdomen was soft. The liver was moderately enlarged. There was a 2+ sacral edema. In the pelvis a small nodule was palpated in the left fornix, possibly the left ovary. Rectal examination was negative. A *hard lymph node* was felt in the left axilla.

Examination of the blood revealed a hypochromic anemia with a moderate leukocytosis; the urine showed a 2+ albuminuria and 0.2% sugar. The blood Wassermann reaction was negative.

The axillary lymph node was excised. On section it showed metastatic carcinoma. A bronchoscopy performed on June 8, 1939, revealed the presence of a granuloma in the left bronchus. The right bronchus was normal.

Comment. In this case the main diagnosis rested between a polyserositis and a malignancy of the pleura. The serial sedimentation of erythrocytes test pointed in the direction of the correct diagnosis 10 months before the biopsy definitely confirmed it.

Discussion. The application of the sedimentation rate of erythrocytes test to the diagnosis of malignancy is not new.[1] Heretofore the rapidity of the sedimentation rate was regarded as the diagnostic factor in the use of the test. However, as it can be shown readily that many cases of undoubted cancer are accompanied by slow sedimentation rates, the usefulness of the test as a diagnostic procedure becomes limited.

The method described here does not depend on the rapidity of the sedimentation rate, but on the maintenance of a certain sedimentation rate level throughout a period of 24 hours.

What is the basis of this test? It has been suggested[3b] that the exceptional behavior of the sedimentation rate of blood depends on changes in the red blood cells in patients suffering from malignant tumors, whereby its property of retaining potassium ions for a long period when stored with its plasma is altered; whereas the cell from the non-cancerous patients does not possess this property. But the experimental evidence brought forth to demonstrate the above-mentioned assumption is insufficient. A small number of our own experiments also failed to corroborate it. Thus the basis for this test remains unexplained, and therefore the mechanism, whatever it is, remains to be determined.

Regarding the practical value of this test, however, we feel that the data of Koster, corroborated in this work, justify the hope that it may become a real aid in the diagnosis of malignant disease.

Many questions are yet to be answered before the usefulness of this test can be fully appraised. The most important question is that dealing with the effect of drugs on the character of the sedimentation curve. In the course of our study we noticed that sulphanilamide and sulphapyridine influence the sedimentation curve in a manner similar to the drugs enumerated by Koster. Another question is how soon after a malignant growth has started in the body does the sedimentation curve become affected and how soon after the removal of that growth does the curve change its character.

Many more questions suggest themselves, but answers must be deferred to future studies.

Our purpose has been to investigate the data of Koster in order to find out whether the serial sedimentation rate by his method may be of value in the diagnosis of malignant tumors. We believe that the data presented warrant an affirmative answer.

Summary. A study was made of 176 cases, of which 118 were proven malignancies and 55 were pathologic conditions other than malignancies. The percentage of positive results (maintenance of the sedimentation rate) in the malignant cases was 95.7% and of negative results was 94.6% in the cases of non-malignant disease. Data are presented to show that the maintenance of the sedimentation rate of erythrocytes in drawn blood over many hours (Koster method) may be of much practical value to the clinician as an aid in diagnosis of malignant tumors and Hodgkin's disease. The reason for this exceptional behavior has not been explained.

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(2.) **Ham, T. H.**, and **Curtis, F. C.**: (*a*) Medicine, **17**, 457, 1938; (*b*) Ibid., p. 462.
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BOOK REVIEWS AND NOTICES

CLINICAL PARASITOLOGY. By CHARLES FRANKLIN CRAIG, M.D., M.A. (HON.), F.A.C.S., F.A.C.P., Colonel United States Army (Retired), D.S.M., Emeritus Professor of Tropical Medicine in the Tulane University of Louisiana, New Orleans, and ERNEST CARROLL FAUST, M.A., PH.D., Professor of Parasitology in the Department of Tropical Medicine, Tulane University of Louisiana, New Orleans. Pp. 772; 244 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, $8.50.

THE second edition of this book within three years after its first appearance indicates very well the place that it fills in the literature of parasitology. This edition has been increased by some 40 pages, part of which is occupied by a new chapter on the leeches (Hirudinea). The character of other changes do not warrant detailed consideration. It is enough to say the book certainly is the equal of any available today. H. R.

THE SOLDIER'S HEART AND THE EFFORT SYNDROME. By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician, University College Hospital; Honorary Consulting Physician to Ministry of Pensions, etc. Pp. 103. Second edition. London: Shaw & Sons, Ltd., 1940. Price, 8s, 6d.

THIS concise practical manual on heart disease in soldiers covers the subject from the examination of recruits to making medical reports at the time of their discharge. Five of the eight chapters deal with the effort syndrome. They contain a description of the condition; a discussion of methods by which it can be diagnosed, and its severity determined; also valuable hints concerning the recognition of malingery. The chapter on prognosis and treatment is based upon follow-up studies of individuals who had the effort syndrome during the first World War. The follow-up period covers only the first five years after discharge, so there are no figures concerning the liability of these individuals to degenerative cardiovascular disease.

There is no better book on the subject. It should be especially useful to officers in the Army Medical Corps who are called upon to make decisions in the field of heart disease. F. W.

MANAGEMENT OF THE CARDIAC PATIENT. By WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., Assistant Professor of Medicine in Charge of the Department of Cardiology, Woman's Medical College of Pennsylvania, Philadelphia; Cardiologist, Women's College, Memorial, Northeastern Hospitals, and Philadelphia Hospital for Contagious Diseases, etc. Pp. 705; 255 illustrations. Philadelphia: J. B. Lippincott Company, 1940. Price, $6.50.

MANY books are recommended as being particularly useful to the general practitioner. Few can be said to fulfil their promise; this one does.

It is an inclusive treatise on heart disease, giving details of management, and presenting many illustrative case reports. Certain sections have been written for the author by recognized authorities in their especial fields. Clarity and sound judgment characterize the book. By way of minor

criticism, it is regretted that sulfapyridine was not given sufficient credit for the part it played in the recovery of a patient having pneumococcic empyema and pericarditis, and known to the Reviewer (p. 175). Orthostatic hypotension is not included among the rarer causes of syncope, nor is the disorder always characterized by "no compensatory increase in the pulse rate" (p. 434). W. J.

THE VIRUS. Life's Enemy. By KENNETH M. SMITH, F.R.S. Pp. 176; 1 illustration. New York: The Macmillan Company, 1940. Price, $2.00.

THE importance of viruses as disease-producing agents is becoming ever more widely recognized. But it is only during the past twenty years that decisive progress has been made in our knowledge concerning these pathogens. Indeed it is probable that many physicians, who graduated as recently as 10 years ago, heard no lectures on viruses during their medical school days. In any case it is quite certain that the medical profession in general is inadequately informed, and for this reason it is desirable to have available a brief but accurate text which may serve as an introduction to the relatively new science of viruses.

The author is a well-known investigator at one of the virus research centers in Great Britain. He has been able to bring together a readable, instructive and thoroughly modern account of the viruses, their nature and their action. His book may highly be recommended to physicians and biologists in general as a good first guide to a fascinating and important group of things. B. L.

A MANUAL OF THE COMMON CONTAGIOUS DISEASES. By PHILIP MOEN STIMSON, A.B., M.D., Assistant Professor of Clinical Pediatrics, Cornell University Medical College; Visiting Physician, Willard Parker Hospital, etc. Pp. 463; 54 illustrations and 6 plates (4 in color). Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, $4.00.

AN excellent, practical and convenient little volume that is highly recommended both to practitioners and students. A third edition testifies to its popularity. R. K.

PHYSICAL DIAGNOSIS. By WILLIAM NANCE ANDERSON, B.Sc., M.D., Associate Clinical Professor of Medicine at the University of Southern California School of Medicine, Los Angeles. Pp. 424; 92 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $4.75.

FOLLOWING a chapter of historical background, Part I, Fundamental Principles of Physical Diagnosis, opens with a discussion of the clinical history and its interpretation. The next 64 pages are devoted to the four common methods of examination—inspection, palpation, percussion, and auscultation—under both normal and abnormal conditions. The physical principles which underlie the production and alteration of sound in the normal and in the diseased lung are not stressed, although the author does include several quotations from Skoda's works.

Part II, on the Physical Examination, begins with an excellent section on general impressions, the head, the neck, and the extremities—those parts so often slighted by students, whose chief interest centers in examination of the thorax. The chapters devoted to the heart and the lungs amplify points already covered in Part I. A section on Special Examinations describes briefly such assorted procedures as genito-urinary and rectal examinations, gastric analysis, the rudiments of neurologic examination, ophthalmoscopic and laryngoscopic examinations, roentgenologic study of the thorax and abdomen, and electrocardiography.

Part III, comprising more than a third of the book, is devoted to Physical Diagnosis in Disease. Here the author attempts to describe the important clinical features and physical findings present in over 200 diseases and pathologic conditions; the individual sections vary in length from several pages to a few lines. S. L.

A Textbook of Laboratory Diagnosis. With Clinical Applications for Practitioners and Students. By Edwin E. Osgood, M.A., M.D., Associate Professor of Medicine and Head of the Division of Experimental Medicine, University of Oregon Medical School, and Member of the Staff of Multnomah County Hospital, etc. Pp. 676; 27 text illustrations and 9 colored plates. Third Edition. Philadelphia: The Blakiston Company, 1940. Price, $6.00.

As in previous editions, the subject matter of this book has been divided into two parts. In Part One the disorders of the different systems are considered with a brief discussion of the essential points in the anatomy, physiology, biochemistry and pathology at the beginning of the respective chapters. Part Two deals with laboratory methods and includes an Index by Diseases, which is a valuable aid in the rapid planning of a laboratory study, and an Author Index in addition to the Subject Index. The chapters on hematology have been revised into three parts with additions made to each division. The author has attempted to clarify the confused nomenclature of the erythropoietic system and with good reasoning has chosen new names for cells of different series. Fortunately, the more commonly used term is given in parentheses after the newer terminology so that the reader can familiarize himself with the latter without frequent reference to an explanatory table at the beginning of the chapter.

In the discussion of the examination of the bone marrow, the technique and interpretation of sternal aspiration is given with no mention of the method of removing a button of sternal marrow for histologic sectioning and differential staining. In inexperienced hands the interpretation of material obtained by aspiration from the marrow, spleen or lymph nodes may meet with considerable difficulty and surely the removal of a lymph node for histologic section would be preferable, under most circumstances, to a needle puncture of the node.

These minor criticisms are more than compensated by the clear presentation of a great deal of material in a relatively brief manner. Where more information might be desired on a given subject, frequent references to recent literature are placed at the bottom of the page and an additional bibliography is included at the end of each chapter. The 9 colored plates are excellent. The book is highly recommended as a guide in laboratory diagnosis and procedure. H. D.

Textbook of Biochemistry. By Benjamin Harrow, Ph.D., Professor of Chemistry, City College, College of the City of New York. Pp. 439; 88 illustrations. Second Edition, revised. Philadelphia: W. B. Saunders Company, 1940. Price, $3.75.

This second edition is enlarged to include more complete discussion of some subjects (enzymes, foods, hormones, sterol chemistry, protein structure, etc.) and to incorporate new material such as our new knowledge of the chemical constitution of the virus of tobacco mosaic, and of bacteriophage, progress in the chemistry of the vitamins, the use of isotopes in metabolism studies, and so on.

Students of the medical sciences will find the book most useful. It is simply and clearly written, and the references at the end of each chapter to the current literature encourage the reading of reviews and original papers. E. W.

THE VARIETIES OF HUMAN PHYSIQUE. An Introduction to Constitutional Psychology. By W. H. SHELDON, PH.D., M.D., Harvard University. With the collaboration of S. S. STEVENS, PH.D., Harvard University, and W. B. TUCKER, M.D., University of Chicago. Pp. 347; 104 illustrations. New York: Harper & Bros., Publishers, 1940. Price, $4.50.

OBSERVATION of variations in human build, and interest in the relation of such variations to temperament and to disease susceptibility, are as old as science. Sheldon and his associates start with the old divisions into phthisic and apoplectic, asthenic and pyknic, and develop the concept of three principal morphologic components of physical build combined in varying degree to produce a large number of recognizable physical types. Their first component, endomorphy, "means relative predominance of soft roundness"; the second component, mesomorphy, "means relative predominance of muscle, bone, and connective tissue"; and third, ectomorphy, "means relative predominance of linearity and fragility." They then assign arbitrary grades to the proportion of each component in the physical makeup of an individual, rating the grades by numbers from one to seven. Thereby, they arrive at a large number of "somatotypes," each identified by a number expressing the relative proportion of each component (*e. g.*, 711, 325, and so on). Some of these somatotypes are of only theoretical occurrence; they describe the actual observation of 76. In addition, they consider variables such as gynandromorphy, or the bisexuality of a physique, and texture, or degree of fineness or coarseness of structure. The authors have developed their own anthropometric method which depends on the measurement of photographs taken under standard conditions. Heretofore, techniques in physical anthropometry have been based upon the methods of Rudolf Martin, which use bony points as landmarks for measurement. Sheldon's technique is thus a radical departure, as it depends upon the measurements of soft part outlines in the photograph more than osseous landmarks. In their technique of anthroposcopy it is necessary to grade the degree of various components by inspection of the photograph as well as by consideration of derived indices. The possibility of lack of objectivity is obvious, but the authors go to great length to explain the precautions they have developed against this disadvantage. Their subjects consisted largely of college students, presumably healthy males in the late 'teens and early twenties; they made only occasional excursions into studies of later years, pathologic states, and the opposite sex. After an extensive description of their somatotypes, the authors set themselves to highly interesting speculations upon such aspects as the problem of norms; the influence of heredity; the influence of endocrine function; the relation of the constitution to temperament, to mental disorder, to susceptibility to physical disease, and to many other variables in the human organism. For instance, the authors suggest that proper diet for one somatotype may be another somatotype's poison; that constitution as well as temperament influence choice in clothing and taste in architecture. They see possibilities for avoidance not only of crime but of domestic discord, if one can predict from an individual's somatotype, and hence his temperament, what worldly pitfalls he should avoid or what type of young woman he should seek out as a mate.

The authors do not pretend to have reached any conclusions. To be complete such study must proceed over a period of years and encompass many, many thousands of observed subjects—possibly it must span generations. Nevertheless a question which has attracted scientific and philosophic attention for so long a time as has this question of the relation of physical build to temperament and disease, deserves unlimited work and perseverance, if only these are feasible.

This is a fascinating book; a bit heavy it may be, but not dry. After

reading a few chapters the Reviewer found himself trying to guess at the somatotypes of patients, of colleagues, and of casual strangers on the street. The style is, in view of the long detailed descriptions of types, remarkably clear, concise, and at times even sparkling. The many photographs of somatotypes supplement the descriptions well, but some of these photographs seem to have lost detail in the process of reproduction. The paper and type are satisfactory for easy reading. J. C.

HEIL HUNGER! HEALTH UNDER HITLER. By DR. MARTIN GUMPERT. Translated from the German by MAURICE SAMUEL. Pp. 128. New York: Alliance Book Corporation, 1940. Price, $1.75.

ACCORDING to the claim made on the wrapper, this volume "studies the effect of the Nazi régime on the health of the German people. Setting aside discussion of political, racial, or religious controversies, it shows clearly the degeneracy and illness that have resulted from the present situation in Germany. For six years Germany has lived under what amounts to war-time conditions and is today found in such a weakened physical state that it is doubtful if her people can from a physical standpoint endure much more privation" . . . . It is stated furthermore that the "book is based exclusively on . . . . medical statistics in technical German magazines and the like. Neither propaganda material nor mere suspicion colors his findings."

Even if these claims were thoroughly substantiated in the text, it is difficult to understand how and why such a volume could be interesting to intelligent persons living in a neutral nation. Maybe the implication is that the horrible example here set up should warn all other people against the system which has produced the results culled out of "medical statistics in technical German magazines . . . ." Sometimes, however, our reactions are conditioned on reflexes which cannot be foretold. The bare facts (if statements found in this volume ever were factual) without the added ingredient, against which the author protests, might arouse emotions not at all intended—they might have excited profound pity in us. We might even have gone to the extent of raising funds to buy arch supports for the greatly increased numbers of people who are now found to have flat feet. As a matter of fact the "added ingredient" is not omitted. It is obviously expected of the reader that he shall go through these pages with mounting disgust.

Whether or not readers are likely to have been found, who were so uncritical as to react at all, in either direction, is to this Reviewer the only serious question there is about the book—and this is one not serious. Statistical studies and reports are, we like to believe, based upon canons which are inviolable. This volume violates nearly all of them.

A. H.

THE HYPOTHALAMUS and Central Levels of Autonomic Function. Proceedings of the Association December 20 and 21, 1939, New York. Vol. XX of Research Publications Association for Research in Nervous and Mental Disease. Editorial Board: JOHN F. FULTON, M.D., Chairman, S. WALTER RANSON, M.D., ANGUS M. FRANTZ, M.D. Pp. 980; 319 illustrations and 35 tables. Baltimore: The Williams & Wilkins Company, 1940. Price, $10.00.

THE reader is impressed by the amount of work that has been accomplished in just one narrow field of medicine in the 30 years that have passed since the first investigations into the significance and physiology of the hypothalamus commenced. The present volume lists more than 1300 references, an average of one paper on the hypothalamus a week during the

last 30 years. The book unites 35 contributions to anatomy and physiology of the hypothalamus and its clinical syndromes, read before the last meeting of the Association for Research in Nervous and Mental Diseases. In the first part phylogenetic and embryologic development of the hypothalamic region are discussed, the arrangement of its nuclei and their connections with other parts of the nervous system and the pituitary gland. In addition, 20 photomicrographs of various planes of the hypothalamus show the exact location of its nuclei in several animals and man. A commission has organized for the first time the confused nomenclature of the structures of this area. The second part of the volume deals with the rôle of the hypothalamus in regulating temperature, water, fat and carbohydrate metabolism, cardiovascular and gonadotropic function, and also with the hypothalamic control of pituitary function. The third part of the symposium is concerned with pathologic changes observed in the hypothalamus in organic diseases and major psychoses, and conversely with clinical syndromes occurring in hypothalamic diseases and tumors. More than 300 photomicrographs, drawings and diagrams illustrate the articles. This is a book for specialists, such as neuroanatomists, neurophysiologists and clinical neurologists; it will be indispensable to them as an invaluable source of information and as a starting point for further research.

F. L.

INJURIES OF THE SKULL, BRAIN AND SPINAL CORD. Neuropsychiatric, Surgical, and Medico-Legal Aspects. Edited by SAMUEL BROCK, New York University. Contributors: BERNARD J. ALPERS, ABRAM BLAU, KARL M. BOWMAN, SAMUEL BROCK, JEFFERSON BROWDER, BRONSON CROTHERS, LEO M. DAVIDOFF, THOMAS K. DAVIS, CHARLES DAVISON, CORNELIUS G. DYKE, CHARLES A. ELSBERG, A. R. ELVIDGE, E. D. FRIEDMAN, FRANCIS C. GRANT, CLARENCE C. HARE, GEORGE B. HASSIN, MOSES KESCHNER, MAX M. PEET, W. RITCHIE RUSSELL, PAUL SCHILDER, C. P. SYMONDS. Pp. 632; 63 illustrations. Baltimore: The Williams & Wilkins Company, 1940. Price, $7.00.

THIS book is a pertinent contribution to one of the increasingly urgent problems of the day—head injuries. Traffic accidents, industrial traumata, war injuries and their economic and forensic implications concur in stressing the need for an authoritative guide through the intricate system of their diagnosis, their immediate and later surgical, medical and psychiatric treatment and through the aftermath of justified and unjustifiable compensation and indemnity claims. Twenty-two specialists have contributed their experience in the various phases of the problem. Alpers discusses birth injuries to the brain, Bronson Crothers to the spinal cord, both pointing to the not sufficiently accepted responsibility of the obstetrician and the inherent risk of spontaneous and instrumental trauma to skull and vertebræ during birth; on the other hand, they reduce to correct proportion the overemphasized rôle of asphyxia as an etiologic factor of retarded development imbecility. The greater space is naturally dedicated to brain injuries proper and their sequelæ. Samuel Brock gives a survey of the whole problem. He discusses the divergent nomenclature, the specific requirements of the history, of the methods of examination and treatment and coördinates the different chapters. G. B. Hassin describes and illustrates the histopathologic changes underlying concussion, contusion and vascular lesions. Jefferson Browder outlines the topic of fractures of the skull, the complicating osteomyelitic infections and epidural abscess; and C. G. Dyke the roentgenologic aspects of skull fractures, aided by 26 instructive Roentgen ray pictures. A detailed chapter by C. P. Symond deals with concussion, contusion of the brain in terms of neurophysiology and pathology, with the specific means of obtaining a correct diagnosis, and with the

treatment of the basic condition as well as of accompanying symptoms and signs. W. R. Russell treats of the injuries of the cranial nerves; E. D. Friedman of traumatic intracerebral hemorrhages. M. M. Peet debates the important question of extradural and subdural hematomata and their treatment; F. C. Grant, post-traumatic brain abscess and meningitis; L. M. Davidoff, the handling of gunshot wounds and of foreign bodies in the brain, supplementing the experiences of the last war by peace time observations. Post-traumatic epilepsy, neuroses and psychoses are extensively dealt with by A. R. Elvidge, P. Schilder, K. M. Bouman and Abram Blau respectively. The excellent paper of C. A. Elsberg on injuries of the spinal cord and its nerve roots reflects the author's great personal experience. Chapters on the relationship of brain injuries to other organic brain diseases by I. S. Wechsler; of spinal cord injuries to other diseases of the cord by T. K. Davis; of the pathology of spinal cord injuries by Charles Davison; on the effect of electric shock, of fat and air embolism upon the nervous system, and on caisson disease by C. C. Hare round out the subject. The two chapters by Moses Keschner on malingering in connection with and the medico-legal aspects of injuries of skull, brain and spinal cord deserve special recommendation. These complex topics are described so intelligibly and comprehensively in all their medical and juridical ramifications as it can be expected only by someone who is an experienced M.D. and an L.B. at the same time. Useful bibliographies are added to most of the chapters. Whoever in the medical profession is concerned with injuries of the central nervous system and their consequences, including the general practitioner, the internist, neurologist, psychiatrist and surgeon, the obstetrician and pediatrician as well as the pathologist and roentgenologist, the industrial and the insurance physician, will welcome this up-to-date handbook. F. L.

NEW BOOKS.

Methods for Diagnostic Bacteriology. A Complete Guide for the Isolation and Identification of Pathogenic Bacteria for Medical Bacteriology Laboratories. By ISABELLE G. SCHAUB, A.B., Assistant in Bacteriology, Department of Pathology and Bacteriology, The Johns Hopkins University School of Medicine, and M. KATHLEEN FOLEY, A.B., Bacteriologist in Charge of the Diagnostic Bacteriological Laboratories of the Medical Clinic, The Johns Hopkins Hospital, Baltimore. Pp. 313. St. Louis: The C. V. Mosby Company, 1940. Price,$3.00.

The Histamine and Insulin Treatment of Schizophrenia and Other Mental Diseases. By HORACE Hill, M.R.C.P., Medical Superintendent, Laverstock House Mental Home, Salisbury. Pp. 133. Baltimore: The Williams & Wilkins Company, 1940. Price, $1.75.

Surgery of the Hand. By R. M. HANDFIELD-JONES, M.C., M.S., F.R.C.S., Surgeon to Outpatients, St. Mary's Hospital; Senior Surgeon, Florence Nightingale Hospital, etc. Pp. 140; 95 illustrations (several in color). Baltimore: The Williams & Wilkins Company, 1940. Price, $4.50.

Congenital Syphilis. By CHARLES C. DENNIE, B.S., M.D., Professor of Dermatology, University of Kansas Medical School, Kansas City, Kan.; Chief of the Department of Dermatology and Syphilology of Bell Memorial Hospital, Kansas City, Kan., etc., and SIDNEY F. PAKULA, B.S., M.D., Visiting Pediatrician to Children's Mercy Hospital, Kansas City General Hospital, Alfred Benjamin Clinic, and Menorah Hospital, Kansas City, Mo. Pp. 596; 133 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $8.00.

Multiple Human Births. Twins, Triplets, Quadruplets and Quintuplets. By HORATIO HACKETT NEWMAN, PH.D., SC.D., Professor of Zoölogy, University of Chicago. Pp. 214; illustrated. New York: Doubleday, Doran & Co., Inc., 1940. Price, $2.50.

The Neuroses in War. By Several Authors under the Editorship of EMANUEL MILLER, M.A. (CANTAB.), M.R.C.P., D.P.M. (CAMBS.), with a concluding chapter by H. CRICHTON-MILLER, M.D., F.R.C.P. Pp. 250. New York: The Macmillan Company, 1940. Price, $2.50.

Synopsis of Materia Medica, Toxicology, and Pharmacology. For Students and Practitioners of Medicine. By FORREST RAMON DAVISON, B.A., M.Sc., PH.D., M.B., Assistant Professor of Pharmacology in the School of Medicine, University of Arkansas, Little Rock. Pp. 633; 45 illustrations (4 in color). St. Louis: The C. V. Mosby Company, 1940.

The Theory and Practice of Anæsthesia. By M. D. NOSWORTHY, M.A., M.D., B.CH. (CANTAB.), Anæsthetist to Westminster Hospital; Anæsthetist to Grosvenor Hospital for Women; late Senior Resident Anæsthetist, St. Thomas's Hospital, with a Foreword by I. W. MAGILL, M.B., B.CH. (BELFAST), Senior Anæsthetist to Westminster Hospital; Anæsthetist to Brompton Hospital for Consumption and Diseases of the Chest. Pp. 223; 35 illustrations. New York: Chemical Publishing Company, 1940. Price, $4.25.

A Treatise on Medicolegal Ophthalmology. By ALBERT C. SNELL, M.D., Lecturer in Ophthalmology, School of Medicine and Dentistry, University of Rochester; Consultant in Ophthalmology, Strong Memorial and Rochester General Hospitals, etc. Pp. 312; illustrated. St. Louis: The C. V. Mosby Company, 1940.

A Surgeon's Life. The Autobiography of J. M. T. FINNEY. Pp. 396; 1 illustration. New York: G. P. Putnam's Sons, 1940. Price, $3.50.

Taber's Cyclopedic Medical Dictionary Including a Digest of Medical Subjects—Medicine, Surgery, Nursing, Dietetics, Physical Therapy. By CLARENCE WILBUR TABER, and Associates. Pp. 1488; 273 illustrations. Philadelphia: F. A. Davis Company, 1940. Price, Plain, $2.50; Thumb-indexed, $3.00.

Hæmorrhoids and Their Treatment. The Varicose Syndrome of the Rectum. By KASPER BLOND, M.D., Vienna, Formerly First Assistant, Rothschild Hospital, Vienna; Hon. Consulting Surgeon, Municipal Hospital, Vienna, etc. Translated by E. STANLEY LEE, M.S., F.R.C.S., Hon. Assistant Surgeon, Westminster Hospital. Pp. 140; 49 illustrations, many in color. Baltimore: The Williams & Wilkins Company, 1940. Price, $4.50.

NEW EDITIONS.

The Practice of Medicine. By JONATHAN CAMPBELL MEAKINS, M.D., LL.D., Professor of Medicine and Director of the Department of Medicine, McGill University; Physician-in-Chief, Royal Victoria Hospital, Montreal, etc. Pp. 1430; 516 illustrations (48 in color). Third Edition. St. Louis: The C. V. Mosby Company, 1940. Price, $10.00.

"This volume is not intended for the specialist, nor does it aspire to be encyclopedic, but rather for the student and practitioner, to assist them in solving the numerous puzzles and problems with which they are daily confronted. So far as the patient is concerned, disease consists of symptoms. It is for these that he or she consults a physician. They represent the earliest manifestations of disease and therefore are of primary importance. They are the clues to the clinical riddles. For this reason they have been given particular prominence, and where possible their causation has been described and their significance has been pointed out. . . . . I have diverted from the usual custom in textbooks on the practice of medicine and have inserted many illustrations with the hope that these may be more informative than a word description." (From the Author's Preface.) The author has been successful in including the chief advances of the 2 years that have elapsed since the publication of the second edition.

Biochemistry for Medical Students. By WILLIAM VEALE THORPE, M.A. (CANTAB.), PH.D. (LOND.), Reader in Chemical Physiology, University of Birmingham. Pp. 464; 37 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, $4.50.

Rose and Carless Manual of Surgery. American (Sixteenth) Edition. Edited by WILLIAM T. COUGHLIN, B.S., M.D., F.A.C.S., Professor of Surgery and Director of the Department of Surgery, St. Louis University School of Medicine; Surgeon-in-Chief, St. Mary's Group of Hospitals, St. Louis. From the Sixteenth English Edition by CECIL P. G. WAKELEY, D.Sc., F.R.C.S., F.R.S.E., F.R.S.A., F.A.C.S., F.R.A.C.S., Fellow of King's College, London; Senior Surgeon, King's College Hospital; Director of Surgical Studies and Lecturer in Surgery, King's College Hospital Medical School, etc., and JOHN B. HUNTER, M.C., M.CHIR. (CANTAB.), F.R.C.S. (ENG.), Surgeon, King's College Hospital; Lecturer in Surgery, King's College Hospital Medical School, etc. Pp. 1656; 1034 illustrations and 30 plates (some in color). Baltimore: The Williams & Wilkins Company, 1940. Price, $9.00.

The Treatment of Diabetes Mellitus. By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor of Medicine Emeritus, Harvard Medical School, etc., HOWARD F. ROOT, M.D., Physician, New England Deaconess Hospital; Consultant in Medicine, Eastern Maine General Hospital, etc., PRISCILLA WHITE, M.D., Physician, New England Deaconess Hospital; Instructor in Pediatrics, Tufts College Medical School, and ALEXANDER MARBLE, A.M., M.D., Physician, New England Deaconess Hospital; Instructor in Medicine, Harvard Medical School. Pp. 783; illustrated. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, $7.50.

The Story of Vitamin B_1 (Thiamine Hydrochloride, U.S.P.). Compiled by C. R. ADDINALL, PH.D., Director, Library Service Bureau, Merck & Co., Inc. Pp. 72; illustrated. Revised Edition. Rahway, N. J.: Merck & Co., Inc., 1940.

Practical Handbook of the Pathology of the Skin. An Introduction to the Histology, Pathology, Bacteriology and Mycology of the Skin with Special Reference to Technique. By J. M. H. MACLEOD, M.A., M.D., F.R.C.P. (LOND.), Physician and Hon. Director of the Pathological Department, St. John's Hospital for Diseases of the Skin; Physician for Skin-Diseases to the Hospital for Tropical Diseases, London, etc., and I. MUENDE, M.B., B.S., B.Sc. (LOND.), Pathologist in charge of Out-Patients' Clinic and Lecturer in Pathology, St. John's Hospital for Diseases of the Skin; Dermatologist to the Middlesex County Council, Willesden General Hospital, etc. Pp. 415; 125 black and white and 27 colored illustrations. Second Edition. New York: Paul B. Hoeber, Inc., 1940. Price, $9.00.

Landmarks and Surface Markings of the Human Body. By L. BATHE RAWLING, M.B., B.CH. (CANTAB.), F.R.C.S., Consulting Surgeon to St. Bartholomew's Hospital. Pp. 98; 36 illustrations. Eighth Edition (New Terminology). New York: Paul B. Hoeber, Inc., 1940. Price, $3.00.

Recent Advances in Endocrinology. By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 432; 67 illustrations including 3 plates. Fourth Edition. Philadelphia: The Blakiston Company, 1940. Price, $5.00.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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WEATHER AND THE CLIMATE.

THE importance of the effect of weather and the climate on the human being was recognized and described more than 2500 years ago by Hippocrates, the world's first meteorologist. It was he who insisted that basically all disease was due to interference with processes which currently are known as "oxidation," and that in the mechanism involved we were dealing with changes in the blood-vessels. This clinical observation 25 centuries ago is as true today as it was then.

In recent years the climatic factor, as expressed in terms of the season and the weather, has received the careful attention of a number of American and European investigators. Since the season and the weather function together as a constant environmental factor from the time a human being is conceived to the time he dies, the fact that they can be measured with a great deal of accuracy constitutes a distinct advantage. Of course, other environmental factors—diet, emotion, infection, fatigue and intoxication—influence an individual, but to evaluate them is often extremely difficult. Definite alterations, for example those involved in daily changes of temperature, are measurable, although there may not always be an absolutely uniform effect from meteorologic changes, since individual members of a community may protect themselves to different degrees. Not only can daily temperature changes be measured, but likewise barometric pressure, daily sunshine, daily precipitation and daily average wind velocity.

Every physiologic adjustment that is induced by weather alteration is apt to find reflection in any region of the body that is inadequate. This expresses itself either in unusual symptomatology, in change of function, or in actual lesions in the various organs of the body—factors that can be measured. Consequently, investigators have been able to measure not only the stimulus, *i. e.*, the weather, but also the effect of that stimulus upon the human being, *i. e.*, the clinical, biochemical and

vasomotor changes that are produced in the human being. Petersen[9] describes the vasomotor and biochemical changes that are induced in the population when a polar air mass passes over a population group. At first the capillaries are less permeable, the blood pressure is increased, the tissues are less hydrated, and the blood is relatively more alkaline (CO_2 content decreased, blood pH increased). In general, this might be called a period of sympathicotonia which finds its reflection in the peripheral tissues, including the mucous membranes of the nose and throat. Gradually the vascular spasm is dissipated, the vessels become dilated to accommodate the increased demand of the organism for greater oxygen consumption, the blood pressure falls, the membranes become more permeable, and the tissues become relatively more acid and hydrated. At this time, presumably, the opportunity for bacterial penetration is greater.

In the field of contemporary otorhinolaryngologic studies, Podvinec[11] describes the climatic factors present in otolaryngology, while Amelung[1] shows the dependence of colds on climate and weather. A series of recent investigations by Sargent[13a,b,c] concerning the common cold and the weekly and seasonal trends of upper respiratory infections in a group of 2000 students indicate that in normal young men observed from day to day under normal conditions of activity and subject to the same meteorologic conditions, the initiation of a "cold" or "sore throat" is always seen to be preceded by an episode involving a fall in daily atmospheric temperature. The first stage of infection from the mucous membranes includes not only the presence of a suitable virus but the coincident biologic phase that makes penetration possible. The rôle of the weather in the etiology of a sudden epidemic of tonsillitis is discussed by Yamasaki.[14] Nineteen cases of acute tonsillitis in children, each child sufficiently ill to warrant hospitalization, are presented by Fabricant[3a] to illustrate the significance of the onset of the "cold front" in precipitating the disease. The precipitation of acute tonsillitis in children most often takes place in the wake of a "cold front," a time when the air temperature falls, the barometric pressure increases, and there is lessened humidity. At this time there is a change in the functional status of the mucous membranes of the nose and throat. A latent period or "lag" of a few hours to one or more days may occur before the actual initiation of the clinical symptoms.

The possibilities of experimental meteorobiologic research are illustrated by Preuner's[12] report of the effect of weather conditions on experimental asthma in guinea pigs. Reporting the results of allergic tests performed during the course of 5 years in a university clinic on 87 children presenting bronchial asthma or bronchus spasms, Becker[2] found that 25% of the children were susceptible to seasonal change or foggy weather. In a study of hay fever among the Japanese, Hara[4] emphasizes the rôle of the weather in precipitating the clinical symptoms. The nasal-bulbar route as a portal of entry for poliomyelitis is well known. Petersen and Mayne[10] believe that among the conditioning factors upon which individual susceptibility in poliomyelitis depends, the meteorologic situation plays an important rôle. The period of prodromal symptomatology is often initiated by the passage of a cold air mass, as is the final precipitation of the paralysis. Both a study of individual case records and the statistical evaluation of the non-epidemic

precipitation of cases in Chicago and of the New York epidemics of 1916 and 1931 make evident this association.

That there are seasonal variations in the incidence of acute purulent otitis media is maintained by Olaison.[7] The relationship between acute mastoiditis and the weather are discussed by both Kimura[5] and Fabricant.[3b] Lynch[6] finds that the greater prevalence of mastoiditis in the northern part of the United States is due to the cold climate which causes lowered resistance to the streptococcus and an increased virulence of that organism. Streptococci from different geographic regions and guinea pigs subjected to artificial climates typical of these regions were used by the author to find why the number of cases of mastoiditis increased steadily from the southern climes to the north. Peller, Stephenson and Souder[8] point out that in the United States Army and Navy the incidence of cutaneous and lip cancer had been found to be several times higher and that of internal cancer substantially lower, than for a comparable group in the civil population of such cities as New York, Chicago, London or Vienna. The authors conclude that the high frequency of cancer of the skin and lip and consequently the low frequency of internal cancer in the Army and Navy depend essentially on the exposure to dermotropic climatic conditions in childhood, adolescence and manhood. Exposure to actinic conditions during adolescence and youth seems more important in its effect on the frequency of surface cancer and the total cancer mortality than is exposure during manhood.

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NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF

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EVALUATIONS OF PSYCHOANALYSIS.

IT would seem appropriate at this time to review the attempts to estimate the permanent significance of the work of Freud. His death has given renewed impetus to these attempts at evaluation both for

therapy and for psychologic theory. Recent literature contains a number of interesting contributions which approach the issue by varied techniques and from varied perspectives.

The report of Kessel and Hyman,[8] with the subsequent additional report by Hyman,[7] consider the value of psychoanalysis as a therapeutic procedure as viewed by internists who refer patients from their general practice to specialists. In presenting their data they defined: *a*, the qualification for a psychoanalyst; *b*, a concept of what constitutes an analysis; and, *c*, a description of the type of clinical material referable to the psychoanalyst for the analysis. In *a*, a psychoanalyst should be a licensed physician who has had a general internship, has himself been analyzed and has completed two control analyses and has been accredited by the psychoanalytical society with which he is affiliated. In *b*, the analysis has required the attendance of the patient for hourly visits from 3 to 5 times a week over a period of time extending from 6 to 24 months and usually averaging 16 months. In *c*, clinical material consisted of patients suffering from frank psychoses such as schizophrenics, manic depressives, insanity and the symptomatic psychoses, patients with behavior problems and maladjustments, patients with simple neuroses such as anxiety and compulsion states and patients with visceral symptoms of a functional nature.

The final report summarizes the results as they were evaluated in 43 patients. Of these 43 patients, 15 suffered from profound psychiatric disease. Of these 15 treated, 12 were considered to be "dismal failures," 2 had results that were still questionable and 1 had a specific therapeutic triumph. Twenty-eight patients suffered psychiatric disorders of minor degree. Of these 28 patients, 17 were distinctly benefited. In 4 of the 17, the analytic cure could be applauded without reservation. In the remaining 13 of this group, improvement was definite but it was felt that the therapeutic result may possibly have been brought about or materially aided by alterations in the life situation apart from the analytical procedure. The remaining 11 patients experienced no significant benefit from their analysis. To recapitulate, of 43 patients treated, 23 were considered failures, 2 had outcomes of doubtful value, 5 were successes with unreserved endorsement of psychoanalysis as the therapeutic agent and 13 were successes with qualified endorsement of psychoanalysis.

Another approach to the problem is to be found in the report by Myerson[10] on the attitude of neurologists, psychiatrists, and psychologists toward psychoanalysis. A questionnaire was drawn up and sent to a group of leading psychologists connected with universities, to the officers and every third member of the American Neurological Association, to the officers and every tenth member of the American Psychiatric Association and more or less haphazardly a group of psychoanalysts were canvassed on the assumption that their membership in a psychoanalytical society necessitated only a small sample. The questionnaire asked the recipient to classify himself in one of four groups, namely:

1. Those individuals who completely accepted psychoanalysis.
2. Those who feel very favorably inclined towards it but do not wholly accept it and are to a certain extent skeptical.
3. Those who in the main tend to reject its tenets but feel that Freud has contributed indirectly to the human understanding.

4. Those who feel that his work has on the whole hindered the progress of the understanding of the mental diseases and the neuroses and reject him entirely.

Of 428 questionnaires sent, 307 individuals replied. Of the 97 members of the American Neurological Association who received questionnaires, 75 replied. These were grouped as follows: 5 belonged in Group 1; 8 classify themselves between 1 and 2; 23 stated they belong in Group 2; 4 classified themselves between Groups 2 and 3; 25 declared themselves to be in Group 3; 3 stated that between Groups 3 and 4 was a good enough allocation of their position; 4 totally rejected psychoanalysis and were hostile; 3 were definitely non-committal or equivocal.

Of the 266 members of the American Psychiatric Association canvassed on the basis stated above, 179 replied. Twenty-five classed themselves in Group 1; 15 between Groups 1 and 2; 54 in Group 2; 32 between Groups 2 and 3; 39 in Group 3 rejecting; 8 belong between this group and total rejection; while there was none who completely rejected psychoanalysis as without value. Six were non-committal.

Of the members of the American Psychoanalytic Association, 28 replies were received to 36 questionnaires sent. Of this group, 16 were in Group 1; 4 between Groups 1 and 2; 3 in Group 2; and 5 were skeptical or non-committal.

Of the miscellaneous group, made up mainly of important members of the American Psychological Association and some physiologists interested in psychologic research, 25 replies were received to 29 questionnaires sent. Two accepted psychoanalysis; 5 belonged in Group 2; 6 placed themselves between Groups 2 and 3; 7 placed themselves in Group 3; and 3 between Groups 3 and 4; 2 completely rejected and placed themselves in Group 4.

Thus, in this group of eminent men, having an almost 100% inclusion in Who's Who in Science and in America, the general attitude is more on the rejection side than on the acceptance, and goes a little further in the direction indicated by the position of the American Neurological Association.

The author admitted that the questions were imperfect and did not permit of any complete answer. However, they did permit most writers to classify themselves somewhere in the 4 categories. In expanding his view concerning his own position, which was mainly in Group 3, he states that it is his belief that Freud was a great man, one of the great men of his time. The concrete values of his work appear to Myerson to be, in the main, indirect results of his work. By taking the obscenity out of sex and by emphasizing the struggle within the personality, he has made objective study possible and stimulated research into the human mind. Greater attention must be paid to the details of human life and the concealed human difficulties. Myerson rejects Freud's concept of the consciousness, the free-association technique, the doctrine of infantile sexuality and the whole concept of symbolism.

In a symposium under the title "Psychoanalysis as seen by Analyzed Psychologists," published in the *Journal of Abnormal and Social Psychology*, there is yet another attempt at evaluation of psychoanalysis. This symposium was inaugurated on the assumption that "analyzed"

experimental psychologists should be authoritative judges of psychoanalysis, since they have had training in scientific procedure as well as first-hand acquaintance with psychoanalysis in the rôle of analysand. The following psychologists have contributed to the symposium: Edwin G. Boring, Professor of Psychology, Harvard University; Carney Landis, Psychiatric Institute, Columbia University; J. F. Brown, University of Kansas; Raymond R. Willoughby, Brown University; Percival M. Symonds, Teachers College, Columbia University; Henry A. Murray, Harvard University Psychologic Clinic; Else Frenkel-Brunswik, Institute of Child Welfare, University of California; and David Shakow, Worcester State Hospital.

In addition, two psychoanalysts have contributed: Hanns Sachs, Boston, Mass., and Franz Alexander, Chicago Psychoanalytic Institute.

Following are brief summaries of the papers comprising the symposium:

Boring[2] gives a personal, somewhat autobiographic account of his analysis, the only one of the symposium which was undertaken for primarily therapeutic reasons. The analysis is therefore inevitably judged in terms of its therapeutic success; judged by that standard, it is pronounced a failure. Nevertheless, certain psychoanalytic phenomena which appeared during the course of the analysis are described: the feeling of sacrifice induced by the analysts' fees, the personal liking for the analyst (although the author does not admit that this was "transfer"), the recovery of old memories, the emotional upheavals during the analytic hour, the emotional reverberations after the analysis was terminated.

It is the author's belief that much of the relief derived from his own analysis was the result partly of a change in the situation which had been troubling him—a change which occurred without the influence of psychoanalysis. Beyond this relief, however, he can see little positive help obtained from the analysis. He concludes, in part: "Now, four years after the close of the analysis, I find myself quite uncertain as to whether it has made any important change in me. Too many other things have happened for me to say why I am as I am . . . . True, the analysis has had this advantage: having been analyzed, I can no longer feel that I have left any available stone unturned. But that would be a rather small return for so large an undertaking. . . . . There is so much about this personality of mine that would be better if different, so much that analysis might have done and did not!"

Taking as his point of departure the paper by Boring, Sachs,[14] who served as Boring's analyst, considers the problem of how often a full cure can be achieved through analysis, and how the result compares with the necessary sacrifice of time, exertion, and money. He points out that in the case of Boring's analysis, the analysand presented no specific neurotic symptom; he presented rather a rigid, fully preserved personality structure, which was not receptive to a new way of living, or an entirely different type of emotional life. To attempt a fundamental change of character in this case did not seem advisable to the analyst; hence the "new personality" which the analysand sought was not forthcoming.

On one other point the author defends this analysis. He claims that the changed situation of which Boring speaks constituted a potential

trauma, which might have produced a breakdown, had not psychoanalysis been able to provide a stopgap.

Proceeding to a theoretical discussion of analysis, Sachs holds that a great obstacle to the correct appraisal of the therapeutic value of psychoanalysis is the absence of any objective standard concerning the following: 1, the seriousness and extent of the neurosis; 2, the strength of the forces opposing the therapy (primary and secondary gain, reality-situation, traumatic experiences, etc.); 3, the extent and duration of the therapeutic result. Despite its lacks, however, analysis seems to this analyst to be getting nearer the roots of psychologic problems than is any other current therapy, since it works on causation rather than the surface.

Starting with a statistical statement of his own analytic hours, Landis[9] proceeds to point out certain phenomena which occurred during the course of the analysis, and to explain them in the more usual terms of psychology.

1. *Anxiety.* The author became possessed by an anxiety which pervaded all his activities, in the course of the analysis. He holds that this resulted from the identity which he saw between the analyst and his (the author's) father; he compares his confessional with the analyst to his father's catechizing him for his misdeeds when he was a boy. Such a process following upon the discovery of identical situations has been called by psychologists emotional reintegration.

2. *Irritability.* This was explained as resulting from attempts to explain the author's actions, and the discovery that such attempts were irrational. Having been divested thus of his usual reference points for making decisions, he became irritable when forced to make choices.

3. *Transfer.* The feeling between analysand and analyst is described in this case as respect, rather than love. Again the phenomenon is explained on the basis of viewing the analyst in the father-rôle.

4. *Resistance.* Resistance became so marked after 200 hours of analysis that the analysis was temporarily discontinued. Upon resumption of analytic techniques the resistance was still present to such a marked extent that the analysis was finally discontinued permanently.

5. *Unconscious Memories.* Many forgotten events were recalled during analysis, but were again explained as resulting from the reintegrative process. Confronted with the specific task of mentally reconstructing the past in detail, the analysand is able to do so with unusual completeness.

6. *Dream Analysis.* Dreams were used as starting-points for free association. The analysand found most unusual in this connection his own ability to say unhesitatingly whether the analyst's interpretation of his dream were right or wrong, although he often blocked on giving the interpretation himself.

7. *Neurosis.* It is apparent that the analytic procedure can create a neurosis, as shown in the appearance of such symptoms as anxiety, apprehension, irritation, and resistance. With psychology attaching importance to the creation of "neuroses" in rats, it is time for psychoanalysts to step forward and say plainly that they know how to set up a neurosis in human beings.

Some attention is given to the psychology of the analysts, which the author says lies in the fact that they have something important to say

but no language in which to say it. Since they must stick to analytic jargon, they acquire no technical vocabulary, no technique of scientific reporting.

It is concluded that the psychoanalytic phenomena are as much the result of the particular method used as of the basic personality structure.

Brown[3] submits that psychoanalysis embraces three different fields of endeavor, which must be evaluated separately: 1, a method of psychologic observation (free association, dream analysis, transference); 2, a systematized set of theoretical constructs, to order the psychologic data found by this method; and 3, a method of psychotherapy in which techniques are used in a special sense to change the structure of the human personality.

Much confusion has resulted from the fact that critics attempt to draw implications from one field to another when such conclusions do not follow.

On the basis of his own analysis, the author draws the following conclusions: 1, granted that the rôle of unconscious motivational processes is important in determining human behavior, psychoanalysis is a uniquely successful way of studying them; 2, granted the necessity for theoretical conceptions in systematic science, those of psychoanalysis are the most adequate we have in accounting for the sources and destruction of energy in the integrated behavior of the organism as a whole; 3, when one keeps in mind the difficulties which confront all psychotherapy and also the ambitiousness of psychoanalytic therapy, psychoanalysis has been unquestionably successful with certain types of mental disorder.

Willoughby[17] attempts to reduce psychoanalytic procedures to the operational basis which has become popular in psychology. The author contends that psychoanalysis has made the most impressive observations on affective phenomena in existence: 1, the emphasis on concept of drive; 2, the concept of conflict among drives, now being explored by experimental psychoanalysis; 3, the reaction of the individual when one drive inhibits the expression of another; and 4, the return of an inhibited drive to motor expression when the inhibition is relaxed.

The two phenomena of interpretation and transference are then put on a psychologic basis. It is argued that the basic process in interpretation is identical with problem-solving; more particularly, with sudden insight which occasionally obtains in problem-solving activities. It is likewise argued that transference is reducible to the proposition that similar stimuli evoke similar reactions; the theory of generalization in learning may suffice to explain psychoanalytic transfer.

The author's attitude toward psychoanalysis may be summed up in his own words: ". . . . there is no such 'thing' as 'psychoanalysis.' There is a subject, in the emotional stress engendered by conflicting habit patterns, largely implicit; there is a psychologist, accustomed to think about such topics as learning and frustration, and having a knowledge of and if possible some actual experience with re-educative procedures; and there is an experimental situation, consisting mostly of freedom from irrelevant stimulation. It will not be surprising if from the repeated concurrence of these elements therapeutic habits and formulations arise having some relationship to those that have arisen from similar situations engaged in by psychoanalysts—or teachers, or priests."

Symonds[16] is anxious again to emphasize the difference between psychoanalytic theory and the process of psychoanalysis. Deductions made on the basis of a single analysis, as applicable to a single case, are not so open to question as those made from psychoanalytic theory, as applicable to human being in general.

Since psychoanalysis is concerned with the conflicts within the individual himself, it seems to be a prerequisite to successful education in children. The child cannot be expected to adjust himself in school if he is not relatively free from inner conflicts. Moreover, many of his conflicts are results of attitudes of other persons with whom he is associated. Therefore, it seems clear that many teachers and parents need psychoanalysis, as well as many children.

Such a program is clearly impractical; therefore it becomes necessary for psychologic research to attempt to discover short cuts in the resolution of conflicts. The author points out certain attempts in this direction which have already been made—notably the use of projective techniques in the study of children's problems. For use with adults, group methods seem promising. " . . . the developments of both psychology and psychoanalysis have been drawing more closely together in interest, outlook, and formulation; and now with comparative suddenness psychologists everywhere are ready to embrace psychoanalysis, to put it to rigorous experimental tests, and to determine exactly what it contains of value to be incorporated into psychological theory."

Murray[12] gives an autobiographic sketch of the author's student days, illustrating his shifts from medicine to psychoanalysis, and ending with a summary of the major psychoanalytic concepts, all told in most amazingly literary style, which must be read to be appreciated. He summarizes, with a possible analytic preference, such concepts as drive, sex, aggression, ego, ego ideal, superego, castration, regression, infantile determination, sublimation. Yet he flays those psychoanalysts who persist in making of their science a cult, pleading constantly for a more closely-knit, esoteric organization. His own suggestion for widening the psychoanalytic structure is a graduate institute of psychology providing education in anatomy, physiology, neurology, scientific method and statistics, clinical psychology and psychoanalysis, general psychology and its special branches, sociology, and anthropology. He quotes Freud as saying that the rightful place of psychoanalysis is with psychology, and upholds him in this feeling.

He concludes with a condemnation of the superficiality that has come to characterize modern American culture—a superficiality which he finds expressed in the attack of psychiatry upon its problems, as well as in psychology. "In contrast to all this shallowness," he says, "there is psychoanalysis, offering its corrective way; and for what it can do here, if for no other reason, I trumpet out its virtues."

Frenkel-Brunswik[6] goes farthest of any in the symposium in attempting to reconcile psychoanalysis with her own system of personality theory. She differentiates, as does her husband, Egon Brunswik, between "central" and "peripheral" layers in personality. The former is the level of overt reaction; the latter, the level of inner forces guiding human conduct. The latter is the more essential part of personality, but study of it has been handicapped because of the difficulty of gaining access to the "central" layers of personality. She makes a second distinction between the immediate effects of peripheral behavior in the

environment, which she calls "proximal," and the more remote results of the individual's activities, which are labelled "distal."

Proceeding from this theoretical framework, Brunswik argues that the major contribution of psychoanalysis is in its provision of an instrument which can be used as a probe into the central portion of the personality. She emphasizes, however, that psychoanalysis begins with the peripheral region, extrapolating from proximal material to the deeper, central material. She, too, emphasizes the importance of projective techniques in getting at the central factors in personality. Examples are given, some from the Adolescent Study at Berkeley, of the application of "central" methods to problems of personality.

Brunswik concludes with a healthy warning against the use of psychoanalysis to get at central factors, with no empirical check on their validity. ". . . . psychological intuitions and interpretations have to be checked back to the mass of surface data. Unless this is done, the data remain without empirical meaning. All the more does this statement hold true for psychoanalysis. The Ego should remain the subject matter of psychology, and extrapolations should be used chiefly in order to throw light back upon the surface phenomena of behavior and achievement. In thus returning ultimately to the surface region, we will have attempted a deep psychology of the surface, rather than indulged in a superficial psychology of the depth."

Shakow[15] became favorably impressed by the psychoanalysts not so much because of what the analysts had to offer, as because of how little the others in the field seemed to offer. At least psychoanalysis presented always for a given patient some hypothesis with which to work. Hence, analysis was undertaken in an attempt to gain some objective basis for evaluating psychoanalysis as therapy. Free association, dream analysis, interpretation, resistance, and transference are described as they were experienced in the analytic sessions.

Shakow interprets analysis as an experiment upon one subject on whom many repeated sessions are available (analogous perhaps to running a single rat through a maze 300 times). It differs from the laboratory experiment, however, in that the analyst takes whatever data comes to hand during the analytic session, while the experimentalist selects his materials beforehand, experimenting on one aspect only of the situation.

From a purely personal point of view, the author feels that he has improved as a person and as a psychologist as the result of his analysis. He is particularly impressed with the sensitization to the great amount of mental activity which goes on beneath the surface, which has resulted from his analysis. He argues also that psychoanalysis offers leads for investigation to the experimentally inclined person. He concludes, "It would seem that the above account indicates almost all profit. For most psychologists I believe this conclusion to be valid if the investment of time and money required is not excessive."

Alexander[1] concludes the symposium with a summarizing statement which is somewhat in the nature of a rebuttal. He thanks the psychologists for their verdict of "not guilty," but interprets that verdict as essentially an act of mercy. "Psychoanalysis is a bad boy but very able, and there is some hope for his improvement."

He argues that psychoanalysis has contributed to a basic issue in psychology: it has developed a method which is adjusted to the nature

of the field of investigation, the human personality. He accuses experimental psychologists of losing sight of the real scope of their field, and of applying experimental methods to inconsequential details within the field of psychology. He points to such theorists as Kurt Lewin and Henry A. Murray as recognizing finally the value of psychoanalysis in psychologic theory, and calls upon the experimental psychologists to examine the Freudian concepts in the psychologic laboratory.

Other experimental psychologists are already at work. Child[4] reports on the relation between measures of infantile amnesia and of neuroticism. Diven[5] has investigated certain determinants in the conditioning of anxiety reaction. Mowrer[11] has investigated the Freudian concept of regression as contingent upon the two factors of fixation and frustration. His experiments were conducted with animals and consequently the behavior reported was considered merely as an analogue of human regression. Rosenzweig[13] has investigated experimentally the concept of repression. In the field of psychosomatic medicine, physiologists are equally active in investigating psychoanalytical concepts. By the application of the principles of the scientific method in the associated areas of interest, the evaluation of psychoanalysis in the field of medicine will properly proceed.

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PHYSIOLOGY

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Locus and Nature of Crossed Inhibition in the Spinal Monkey. GRAYSON P. MCCOUCH, JOSEPH HUGHES, and WINIFRED B. STEWART (Department of Physiology, University of Pennsylvania School of Medicine, and Pennsylvania Hospital for Mental and Nervous Diseases). In spinal cats and dogs crossed inhibition of the ipsilateral flexor reflex is associated with inhibition of the internuncial cord potential of equivalent degree. In the chronically spinal macaque monkey, on the other hand, a crossed afferent volley confined to alpha, beta, and gamma fibers may markedly inhibit the reflex without modifying the internuncial potential. Stronger crossed stimuli may reduce the internuncial potential to lesser or equal degree than the reduction of the reflex response. With suitable grading of inhibitory and excitatory volleys, the crossed component of the internuncial potential from the excitatory

volley proves to be more susceptible to inhibition than the ipsilateral component.

The case in which reflex inhibition occurs without demonstrable change in internuncial potential is of interest in relation to current theories of inhibition. Such theories may be divided into those which refer the reduction in irritability to immediately precedent response of the same units and those which invoke specific inhibitory endings. If such records may be accepted as evidence that excitatory drive upon the motoneurons is not essentially altered, then inhibition has occurred in them in the absence of immediately preceding activity.

The Effect of Bromide Administered to Pregnant Rats on the Learning Ability of the Offspring. B. K. HARNED, H. C. HAMILTON, and J. C. BORRUS (Department of Pharmacology, Woman's Medical College of Pennsylvania, and the Department of Psychology, Temple University). The learning ability of rats born of normal pregnancies was compared with that of siblings born from mothers administered sodium bromide from the fourth through the twelfth day of gestation. The drug was administered in the drinking water and the total amount averaged 192 mg./kilo. The maximal depression produced in the mothers did not exceed a mild apathy.

Analyses of 4-hour-old newborn rats disclosed an average sodium bromide content of 75 mg./kilo. At 21 days of age the animals were weaned and until 40 days of age they were kept on a diet containing 1% of sodium chloride. At the end of this period the average sodium bromide excretion per rat per 24 hours was 1.6 micrograms.

The learning tests, made in a five cul-de-sac maze with the correct pathway consisting of rrllr turns, were started at 60 days of age and after 3 preliminary trials continued 50 days at the rate of one test per day. Errors made and time consumed served as the criteria for learning. There were 23 control and 29 experimental animals with approximately the same distribution of the sexes in the two groups. For the 50 trials the mean number of errors made by the control group was 146 and for the experimental group 178 and the chances that the difference is significant are 94 per 100. The mean time required by the control group for the 50 trials was 1099 seconds and by the experimental group 1701 seconds and the chances that this difference is significant are 96 per 100. The variability of the experimental group was greater than that of the control group in both errors and time. For both criteria the chances are 99 per 100 that the differences between their sigmas are real.

These results suggest that the administration of relatively small amounts of sodium bromide to pregnant rats decreases the learning ability of the offspring.

Studies in Capillary Mobility, Minute Vessel Pressure, and Cutaneous Lymphatic Flow in Arterial Hypertension. R. B. RUTHERFORD, J. Q. GRIFFITH, JR., E. ROBERTS, H. O'B. CORBIT, and M. A. LINDAUER (Robinette Foundation, Hospital of the University of Pennsylvania). Counts of cutaneous capillaries were made in normal subjects, in persons with cardiovascular disease without hypertension, and patients with cardiovascular disease with hypertension. Initial counts were compared with total counts made in the area of a histamine flare. While in many instances there was no difference in the response of

persons with cardiovascular disease and normal subjects, there was a tendency in certain cases of the former for initial counts to equal or approximate total counts after histamine. This was regarded as representing a diminished capillary mobility.

Minute vessel pressure was measured by an indirect technique evolved from the Danzer Hooker method and thought to have certain advantages over it. It is probable that the pressure read is that in the precapillary arteriole, not that in the capillary. The normal range is from 13 to 23 mm. of mercury, most readings lying between 15 and 20. In the flare area of a histamine wheal there is, in the normal subject, a rise of 3 mm. or more. In subjects with hypertension the minute vessel pressure may be normal or increased. After histamine it may rise normally, or the rise may be exaggerated, or there may be no significant change. Patients with diminished capillary mobility frequently show no significant rise in pressure after histamine.

Cutaneous lymphatic flow was measured in normal and hypertensive subjects by the dye method of McMaster. In hypertensive subjects it was found to be either normal or increased. Increased flow was frequently but not invariably associated with increased minute vessel pressure.

Quantitative Studies on the Passage of Protein Molecules Through the Glomerular Membranes. P. A. Bott and A. N. Richards (Laboratory of Pharmacology, University of Pennsylvania). Since normal glomerular membranes in amphibia have been shown to be completely permeable to inulin (molecular weight 5100) and impermeable to serum albumin (molecular weight approximately 70,000), an attempt was made to obtain more definite knowledge as to the nature and limit of permeability of the glomerular membranes by studying the passage through them of proteins with molecular weights between those two. The experiments were of two types: 1, "Direct" experiments (chiefly on Necturi) in which fluid collected from Bowman's capsule was analyzed for protein. Collections were made while kidneys were being perfused with known protein solutions. 2, "Indirect" experiments (chiefly on frogs) in which urine collected from the ureters during perfusion of protein and inulin was analyzed for these two substances, the inulin concentration ratio then being used to calculate the concentration of protein in glomerular fluid.

The protein concentration of glomerular fluid expressed as per cent of that found in perfusion fluid averaged as follows: crystalline hen's egg albumin 57, crystalline duck egg albumin 55, crystalline lactoglobulin 80, and the purified protein derivative "P.P.D." from tuberculin 86 (also, based on fewer experiments: Bence-Jones protein 36 and insulin 25). The tuberculin protein has a molecular weight of about 13,500 while all the others have been regarded as members of the 35,200 molecular weight group. The results of the direct and indirect methods when used with the same protein, agree sufficiently well to exclude the possibility that tubular reabsorption influences results of "indirect" experiments. There was no indication of an increased permeability due to passage of these proteins through the membranes except, possibly, in the case of insulin. Urethane in a concentration of 7% increased permeability.

It is suggested that while filtrability of the proteins may be grossly a matter of size, factors other than size play a part.

Effect of Pantothenic Acid on Growth and Reproduction of Rats on Synthetic Diets. KLAUS UNNA (Merck Institute for Therapeutic Research, Rahway, N. J.). In these studies rats were maintained on a basal diet consisting of vitamin free casein, 18%; dextrose (cerelose), 68%; crisco, 9%; salt mixture No. 1 U.S.P. XI, 4%; and cod-liver oil, 2%, and supplemented daily with 40 micrograms each of thiamin, riboflavin and pyridoxine, 0.5 mg. of nicotinic amide and 5 mg. of choline chloride. A dose of 3 mg. of alpha tocopherol was given once weekly. Unless pantothenic acid is supplied, the rats cease to grow after 4 weeks on this diet, and die within 6 to 10 weeks. The pantothenic acid deficient rats exhibit external symptoms principally noticeable in the change of the condition of the fur coat. If pantothenic acid is supplied in daily doses from 10 to 200 micrograms a graded dose response is obtained in these animals. Daily doses of 100 micrograms meet the growth requirement of the rats on this diet and prevent the appearance of deficiency symptoms. The growth response to a liver preparation supplying adequate amounts of pantothenic acid is greater than that obtained with pantothenic acid alone. This would indicate the presence of unknown and yet unidentified factors in liver. With 10 or 25 micrograms of pantothenic acid daily the animals reached stationary weights. With larger doses growth was continuous and these animals reached maturity. Our first attempt to mate animals receiving 75, 100, 200 micrograms were successful insofar as two litters, one of 7 and one of 5, of normal birth-weight were obtained. These young rats, however, did not gain rapidly in weight in spite of the fact that they were nursed by their mothers. This might be taken as a further indication of the necessity of some other factor supplied in natural foodstuffs, such as liver. Our results show that the incorporation of adequate amounts of thiamin, riboflavin, nicotinic amide, B_6 and pantothenic acid into a synthetic diet free from water soluble vitamins assures continuous growth until maturity and reproduction.

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